Diagnosis and differential diagnosis of rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric, inflammatory, peripheral polyarthritis of unknown etiology. It typically leads to deformity through the stretching of tendons and ligaments and destruction of joints through the erosion of cartilage and bone. If it is untreated or unresponsive to therapy, inflammation and joint destruction lead to loss of physical function, inability to carry out daily tasks of living, and difficulties in maintaining employment.

Early recognition and treatment with disease-modifying antirheumatic drugs (DMARDs) is important in achieving control of disease and prevention of joint injury and disability. However, in patients with early disease, the joint manifestations are often difficult to distinguish from other forms of inflammatory polyarthritis. The more distinctive signs of RA, such as joint erosions, rheumatoid nodules, and other extraarticular manifestations, are seen primarily in patients with longstanding, poorly controlled disease but are frequently absent on initial presentation.

This topic will review the approach to the diagnosis and differential diagnosis of RA. The clinical features of this disorder, its extraarticular manifestations, and laboratory markers that are clinically useful in the diagnosis of RA are discussed in detail separately. (See "Clinical manifestations of rheumatoid arthritis" and "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis".)

EVALUATION FOR SUSPECTED RA

Rheumatoid arthritis (RA) should be suspected in the adult patient who presents with inflammatory polyarthritis. The initial evaluation of such patients requires a careful history and physical examination, along with selected laboratory testing to identify features that are characteristic of RA or that suggest an alternative diagnosis. (See "Clinical manifestations of rheumatoid arthritis" and 'Differential diagnosis' below.)

We focus especially on the following for the purposes of diagnosis:

- We perform a thorough medical history, with particular attention to joint pain, reported swelling, and the presence, location (peripheral joints rather than low back), and duration (at least 30 minutes) of morning stiffness. The absence of other conditions or symptoms suggesting an alternative diagnosis, such as psoriasis, inflammatory bowel disease (IBD), or a systemic rheumatic disease such as systemic lupus erythematosus (SLE), helps to exclude other disorders.

  Symptoms of arthritis that have been present for a short time (for example, less than six weeks) may well be due to an acute viral polyarthritis rather than to RA. The longer symptoms persist, the more likely the diagnosis of RA becomes. Thus, in patients presenting very early, close observation with frequent follow-up appointments is required, with repeated serologic analysis for anti-cyclic citrullinated peptide (CCP) antibodies, rheumatoid factor (RF), and acute phase reactants. In a minority of patients, several such visits are required before the differential diagnosis between RA and viral arthritis becomes established. (See "Clinical manifestations of rheumatoid arthritis", section on 'Typical 'classic' RA' and 'Differential diagnosis' below.)

- A complete physical examination is indicated to assess for synovitis, including the presence and distribution of swollen or tender joints and limited joint motion; extraarticular disease manifestations, such as rheumatoid nodules; and signs of diseases, such as SLE or psoriasis, included in the differential diagnosis. (See "Clinical manifestations of rheumatoid arthritis", section on 'Symptoms and physical findings' and "Rheumatoid nodules" and 'Differential diagnosis' below.)

- We perform the following laboratory tests, which support the diagnosis if positive and/or elevated:

- RF and anti-CCP antibodies – We perform both RF and anti-CCP antibody testing when initially evaluating a patient with suspected RA. The results of both tests are informative, since a positive result for either test increases overall diagnostic sensitivity, while the specificity is increased when both tests are positive. Despite this, both tests are negative on presentation in up to 50 percent of patients and remain negative during follow-up in 20 percent of patients with RA. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Rheumatoid factors' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

- Erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels – Both the ESR and CRP are typically elevated in RA. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Erythrocyte sedimentation rate' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'C-reactive protein'.)

- We perform the following testing in all patients, which may be helpful in the differential diagnosis of RA and as baseline testing for monitoring of disease activity or progression and medication safety:

  - Antinuclear antibody (ANA) testing – A negative ANA helps exclude SLE and other systemic rheumatic diseases; the ANA may be positive in up to one-third of patients with RA. In patients with a positive ANA, anti-double stranded DNA and anti-Smith antibody testing should also be performed; these antibodies have high specificity for SLE. (See "Measurement and clinical significance of antinuclear antibodies".)

  - Complete blood count (CBC) with differential and platelet count, tests of liver and kidney function, serum uric acid, and a urinalysis – The CBC is often abnormal in RA, with anemia and thrombocytosis consistent with chronic inflammation. Liver and kidney testing abnormalities indicate a disorder other than RA; if caused by comorbid conditions, they may affect therapeutic choices or drug dosing. Hyperuricemia may prompt additional efforts, including arthrocentesis and crystal search, to exclude gout; polyarticular gout can infrequently be mistaken for RA. (See "Hematologic manifestations of rheumatoid arthritis", section on 'Anemia of chronic disease' and "Hematologic manifestations of rheumatoid arthritis", section on 'Platelet abnormalities' and 'Differential diagnosis' below.)

- Radiographs of the hands, wrists, and feet – We obtain radiographs during the initial evaluation primarily as a baseline for monitoring disease progression. However, characteristic joint erosions may be observed in patients presenting with symptoms for the first time and, hence, aid in diagnosis. Additionally, in patients with other disorders, such as psoriatic arthritis, spondyloarthropathy, gout, or chondrocalcinosis, radiographic changes more characteristic of these conditions may point to an alternative diagnosis. (See '2010 ACR/EULAR criteria' below and 'Differential diagnosis' below and "Clinical manifestations of rheumatoid arthritis", section on 'Imaging'.)

- We perform the following studies in selected patients:

  - Serologic studies for infection – In patients with a very short history (for example, less than six weeks) particularly those who are seronegative for anti-CCP and RF, we perform serologic testing for human parvovirus B19, hepatitis B virus (HBV), and hepatitis C virus (HCV). In areas endemic for Lyme disease, we perform serologic studies for Borrelia as well. In people who live in or have traveled to parts of the world where mosquito (*Aedes aegypti* and *Aedes albopictus)*-bite transmitted viral diseases are prevalent, chikungunya virus infection should be suspected in patients with fever and arthralgia, as this may be followed by a chronic polyarthritis; diagnosis is confirmed by serologic tests. (See 'Viral polyarthritis' below and "Viruses that cause arthritis" and "Diagnosis of Lyme disease" and "Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis".)

  - Synovial fluid analysis – We perform arthrocentesis and synovial fluid analysis for the diagnosis or exclusion of gout, pseudogout, or an infectious arthritis if a joint effusion is present and if there is uncertainty regarding the diagnosis, particularly in the setting a monoarthritis, oligoarthritis, or asymmetric joint inflammation. Synovial fluid testing should include a cell count and differential, crystal search, and Gram stain and culture. Synovial fluid analysis should also be obtained to exclude infection or crystalline arthropathy in patients who undergo glucocorticoid injections for symptomatic relief. (See "Clinical manifestations of rheumatoid arthritis", section on 'Laboratory findings' and "Synovial fluid analysis".)

  - Magnetic resonance imaging (MRI) and ultrasound – MRI studies and ultrasonography do not have an established role in the routine evaluation of patients with polyarthritis.

However, MRI and ultrasound are more sensitive than radiography at detecting changes resulting from synovitis and may be helpful in establishing the presence of synovitis in patients with normal radiographs and uncertainty regarding either the diagnosis or the presence of inflammatory changes, such as patients with obesity or subtle findings on examination. (See "Clinical manifestations of rheumatoid arthritis", section on 'Imaging'.)

DIAGNOSIS

Our diagnostic criteria — The diagnosis of rheumatoid arthritis (RA) can be made when the following clinical features are all present:

- Inflammatory arthritis involving three or more joints. (See "Clinical manifestations of rheumatoid arthritis", section on 'Symptoms and physical findings'.)
- Positive rheumatoid factor (RF) and/or anti-citrullinated peptide/protein antibody (such as anti-cyclic citrullinated peptide [CCP])) testing. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)
- Elevated levels of C-reactive protein (CRP) or the erythrocyte sedimentation rate (ESR). (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Erythrocyte sedimentation rate'.)
- Diseases with similar clinical features have been excluded, particularly psoriatic arthritis, acute viral polyarthritis, polyarticular gout or calcium pyrophosphate deposition disease, and systemic lupus erythematosus (SLE). (See 'Differential diagnosis' below.)
- The duration of symptoms is more than six weeks.

These criteria are consistent with the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. (See '2010 ACR/EULAR criteria' below.)

The diagnosis of RA may also be made in some patients who do not meet all of our criteria. (See 'Patients not meeting above criteria' below.)

Inflammatory arthritis — Arthritis is typically present in the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands. The wrists are also commonly involved,

as are the metatarsophalangeal (MTP) joints in the feet, but any upper or lower extremity joint may be affected. Symmetric polyarthritis, particularly of the MCP, MTP, and/or PIP joints, strongly suggests RA. Although distal interphalangeal (DIP) joint disease can occur in patients with RA, DIP involvement strongly suggests a diagnosis of osteoarthritis or psoriatic arthritis. (See "Clinical manifestations of rheumatoid arthritis", section on 'Symptoms and physical findings' and 'Osteoarthritis' below and 'Psoriatic arthritis' below.)

Serology — RFs occur in 70 to 80 percent of patients with RA. Their diagnostic utility is limited by their relatively poor specificity, since they are found in 5 to 10 percent of healthy individuals, 20 to 30 percent of people with SLE, virtually all patients with mixed cryoglobulinemia (usually caused by hepatitis C virus [HCV] infections), and in those with many other inflammatory conditions. Higher titers of RF (at least three times the upper limit of normal) have somewhat greater specificity for RA. The prevalence of RF positivity in healthy individuals rises with age. (See "Origin and utility of measurement of rheumatoid factors" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Rheumatoid factors'.)

Antibodies to citrullinated peptides/proteins are usually measured by enzyme-linked immunosorbent assays (ELISAs) using CCPs as antigen. Anti-CCP antibodies have a similar sensitivity to RF for RA but have a much higher specificity (95 to 98 percent) [1-4]. The specificity is greater in patients with higher titers of anti-CCP antibodies (at least three times the upper limit of normal). Another test, anti-mutated citrullinated vimentin, gives similar results to anti-CCP and is used as an alternative in some laboratories [5]. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

Acute phase reactants — Elevations of the ESR and/or CRP level are consistent with the presence of an inflammatory state, such as RA. Normal acute phase reactants may occur in untreated patients with RA, but such findings are very infrequent. The degree of elevation of these acute phase reactants varies with the severity of inflammation. As an example, an ESR of 50 to 80 is not uncommon in patients with severely active RA. By comparison, an ESR of 20 to 30 can be observed with only a few mildly to moderately active joints. Although increased levels of acute phase reactants are not specific for RA, they are often useful for distinguishing inflammatory conditions from noninflammatory disorders that present with musculoskeletal symptoms (eg, osteoarthritis or fibromyalgia). (See "Acute phase reactants" and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Erythrocyte

sedimentation rate' and "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'C-reactive protein'.)

Patients not meeting above criteria — The diagnosis of RA may also be made in patients without all the criteria described in the previous section. Examples include the following:

- **Seronegative RA** – Patients who lack both RF and anti-CCP antibodies may be diagnosed with RA based upon findings otherwise characteristic of RA if appropriate exclusions have been met. Such patients with seronegative RA differ from anti-CCP-positive patients genetically and in their environmental risks, disease severity, and clinical responsiveness to some medications [6]. Additional research is needed to better characterize this population. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis".)

- **Recent onset RA** – Patients with disease for less than six weeks may be diagnosed with RA based upon findings otherwise characteristic of RA, including anti-CCP antibodies, if testing for viral serologies is negative and if other appropriate exclusions have been met. (See 'Evaluation for suspected RA' above and 'Viral polyarthritis' below.)

- **Inactive RA** – Patients without active arthritis or elevated acute phase reactants (eg, due to treatment of recent onset disease or with longstanding disease) may be diagnosed with RA based upon well-documented past findings characteristic of RA, especially in the presence of positive testing for RF and anti-CCP, or typical bone erosions on radiography, and in the absence of an alternative more likely diagnosis.

Patients in the several categories above, and other patients who should be diagnosed with RA but do not meet our standard criteria, will generally have findings that are consistent with the 2010 ACR/EULAR classification criteria for RA [7,8]. These criteria were developed for the classification of patients with RA for the purpose of epidemiologic studies and clinical trials, not primarily for clinical diagnosis. Nevertheless, the same features that are of value in classification tend to be useful for the purpose of diagnosis in clinical practice. Further study is required to establish their utility as diagnostic criteria in general practice. (See 'Classification criteria' below.)

CLASSIFICATION CRITERIA

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism

(EULAR) classification criteria focus on features that would identify patients at an earlier stage of disease than would the previously used criteria that had been last revised in 1987 [7-10]. The 1987 ACR criteria were formulated to distinguish patients with established rheumatoid arthritis (RA) from patients with other defined rheumatic diseases; the 2010 ACR/EULAR criteria for RA focused on identifying the factors, among patients newly presenting with undifferentiated inflammatory synovitis, which could allow for the identification of patients for whom the risk of symptom persistence or structural damage is sufficient to be considered for intervention with disease-modifying antirheumatic drugs (DMARDs) [7,8]. (See below.)

2010 ACR/EULAR criteria — Using the 2010 ACR/EULAR classification criteria for RA, classification as definite RA is based upon the presence of synovitis in at least one joint, the absence of an alternative diagnosis that better explains the synovitis, and the achievement of a total score of at least 6 (of a possible 10) from the individual scores in four domains [7,8,11]. The highest score achieved in a given domain is used for this calculation. These domains and their values are:

- Number and site of involved joints
  - 2 to 10 large joints (from among shoulders, elbows, hips, knees, and ankles) = 1 point
  - 1 to 3 small joints (from among the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists) = 2 points
  - 4 to 10 small joints = 3 points
  - Greater than 10 joints (including at least 1 small joint) = 5 points
- Serological abnormality (rheumatoid factor or anti-citrullinated peptide/protein antibody)
  - Low positive (above the upper limit of normal [ULN]) = 2 points
  - High positive (greater than three times the ULN) = 3 points
- Elevated acute phase response (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) above the ULN = 1 point
- Symptom duration at least six weeks = 1 point

In addition to those with the criteria above, which are best suited to patients with newly presenting disease, the following patients are classified as having RA:

- Patients with erosive disease typical of RA with a history compatible with prior fulfillment of the criteria above
- Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who have previously fulfilled the criteria above based upon retrospectively available data

1987 ACR criteria — It is important to recognize that RA has been defined in virtually all clinical trials of drugs for RA initiated from 1987 through 2010 based upon the criteria developed and validated by the ACR (previously the American Rheumatism Association) in 1987 (table 1) [9,10]. A patient was classified as having RA if at least four of these seven criteria were satisfied; four of the criteria must have been present for at least six weeks: morning stiffness, arthritis of three or more joint areas, arthritis of the hands, and symmetric arthritis. Rheumatoid factor (RF) was included as a criterion, but anti-cyclic citrullinated peptide (CCP) antibody testing was not available at that time. The other two criteria were rheumatoid nodules and radiographic erosive changes typical of RA, but these are generally not present in the early stages of disease.

Thus, while these criteria were very good at separating inflammatory from noninflammatory arthritis, the major drawback of the 1987 criteria has been their insensitivity in identifying some patients with early disease who subsequently develop typical established RA [10]. On the other hand, the criteria did not require any exclusions, and patients could initially fulfill the diagnostic criteria but occasionally evolve into other diagnoses, particularly systemic lupus erythematosus (SLE), Sjögren's syndrome, scleroderma, mixed connective tissue disease, psoriatic arthritis, and crystalline arthritis.

DIFFERENTIAL DIAGNOSIS

A variety of conditions must be considered in the differential diagnosis of rheumatoid arthritis (RA). Features of some disorders that are included in the differential diagnosis of RA are shown in the table (table 2). (See "Evaluation of the adult with polyarticular pain".)

Viral polyarthritis — A number of viral infections may cause an acute viral polyarthritis.

- Viral infections such as rubella [12], parvovirus B19 [13], and hepatitis B virus (HBV) can cause an acute polyarthritis syndrome that may be mistaken for the inflammatory polyarthritis of RA. However, the syndrome is usually short-lived, lasting only from a few days to several weeks, and rarely beyond six weeks. Hepatitis C virus (HCV) can cause a polyarthritis or oligoarthritis in a minority of patients, but is more commonly associated with arthralgias.

  Serologic testing can help identify patients with HBV, HCV, or human parvovirus B19 in some individuals with early disease, but a viral etiology cannot always be excluded until after symptoms are present for at least six to eight weeks in the absence of diagnostic serologic testing for a specific virus (see "Viruses that cause arthritis") Unlike rheumatoid factor (RF) (which may occur in patients with a variety of infections, including HCV infection), anti-cyclic citrullinated peptide (CCP) antibodies are usually negative in patients with HCV infection who do not have RA. (See "Biologic markers in the diagnosis and assessment of rheumatoid arthritis", section on 'Anti-citrullinated peptide antibodies'.)

- Increasingly reported in travelers, alphaviruses are globally distributed mosquito-borne RNA viruses that cause epidemics of polyarthritis/arthralgia [14,15]. Among all of the viruses that can cause arthritis, the alphaviruses are unusual because nearly all symptomatic infections in adults result in joint symptoms. The incubation period lasts from several days to three weeks; infection is typically associated with triad of fever, arthritis, and rash [14]. However, all aspects of the triad may not be present, thereby making the diagnosis difficult.

  One such alphavirus, Chikungunya, has become a global disease with increasing world travel and has caused large outbreaks in Italy, India, Indian Ocean islands, and in the Caribbean region and surrounding countries [16,17]. Patients with more persistent disease can mimic seronegative RA clinically to a sufficient degree to satisfy the 2010 classification criteria for RA if the initial symptoms of fever and rash and history of travel to an endemic region are not appreciated [18]. Serologic studies can help to document exposure to the Chikungunya virus. (See "Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

  Alphavirus infections generally resolve over three to six months. The diagnosis of alphavirus infection can be made by appropriate serologic testing in travelers from endemic areas with persistent arthritic symptoms. (See "Viruses that cause arthritis", section on

'Alphaviruses' and "Chikungunya fever: Epidemiology, clinical manifestations, and diagnosis".)

- A large joint arthritis has been reported in association with human T lymphotropic virus type 1 (HTLV-I) [19]. These infections are sometimes associated with the presence of RFs (usually in low titer), antinuclear antibodies (ANA), and elevated acute phase reactants. HTLV-I infections can generally be distinguished from RA by the finding of specific antiviral antibodies and the typically self-limited nature of arthritis associated with HTLV-I.

Systemic rheumatic diseases — Early RA may be difficult to distinguish from the arthritis of systemic lupus erythematosus (SLE), Sjögren's syndrome, dermatomyositis (DM), or overlap syndromes such as mixed connective tissue disease. In contrast with RA, these disorders are generally characterized by the presence of other systemic features, such as rashes, dry mouth and dry eyes, myositis, or nephritis, and by various autoantibodies not seen in RA. Additionally, the relative responses of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be less well-correlated with each other in other diseases, particularly SLE, than in RA. Whereas both are commonly raised in RA, the CRP is often normal or only minimally elevated in patients with active SLE even when the ESR is elevated.

Taken together, the pattern of longstanding disease, morning stiffness, symmetric arthritis, subcutaneous nodules, and the deformities characteristic of RA does not develop in these other disorders. There are several exceptions to this observation:

- Morning stiffness is common in all inflammatory arthritides. Symmetric arthritis is seen in patients with SLE and can be present in other disorders. Infrequently, nodules similar to those seen in RA may occur in patients with SLE, and other nodular lesions may mimic rheumatoid nodules. (See "Rheumatoid nodules", section on 'Subcutaneous nodules' and "Rheumatoid nodules", section on 'Differential diagnosis'.)

- An erosive arthritis has been described in some overlap syndromes, particularly those associated with anti-tRNA synthetases and anti-U1 RNP antibodies [20]. (See "Clinical manifestations of mixed connective tissue disease".)

- Jaccoud's arthropathy occurs in up to 5 to 10 percent of patients with Sjögren's syndrome or SLE and can also occur in sarcoidosis [21]. (See "Musculoskeletal manifestations of systemic lupus erythematosus" and "Sarcoid arthropathy".)

  The joint deformities of Jaccoud's arthropathy are not caused by destruction of joints but by

loosening and lengthening of periarticular structures and tendons. The ulnar drift or swan neck deformities caused by this disorder resemble RA superficially but can be distinguished by the fact that they are "correctable" on physical examination: fingers with these deformities can be moved manually back into normal alignment. In addition, radiographs in Jaccoud's arthropathy rarely reveal the cartilage loss, erosions, or cysts that are typical of longstanding RA.

Palindromic rheumatism — Palindromic rheumatism is characterized by episodes of joint inflammation sequentially affecting one to several joint areas for hours to days, with symptom-free periods that may last from days to months. Some patients presenting with this syndrome eventually develop a well-defined rheumatic disease, the most common being RA (ranging from 28 to 67 percent); some of the remaining patients develop SLE and other systemic disorders [22,23]. Patients with anti-CCP antibodies appear more likely to progress to definite RA [24,25]. Close follow-up and specific serologic evaluation can help distinguish among these disorders. (See "Clinical manifestations of rheumatoid arthritis", section on 'Palindromic rheumatism'.)

Hypermobility syndrome and fibromyalgia — Pain, rather than stiffness or swelling, is the dominant symptom of the two common disorders, hypermobility syndrome and fibromyalgia [26,27]. Although the hypermobility syndrome and fibromyalgia can both bear superficial resemblances to RA due to the presence of polyarthralgia, there are important distinguishing features:

- The hypermobility syndrome is associated with hyperextensible joints, and patients lack signs of synovitis. (See "Joint hypermobility syndrome".)
- Fibromyalgia is associated with tender points at nonarticular sites and chronic widespread pain. However, there is no evidence of synovitis, such as swelling, warmth, or diminished joint range of motion, although patients may exhibit joint line tenderness on exam. (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)
- Neither the hypermobility syndrome nor fibromyalgia is associated with significant titers of RF or anti-CCP antibodies or with elevated levels of acute phase reactants.

Although RA is normally not difficult to distinguish from fibromyalgia, a significant minority of patients with RA also develop fibromyalgia. The source of complaints in such patients needs to be carefully assessed to distinguish heightened pain sensitivity from pain related to inflammatory joint disease.

Reactive arthritis and arthritis of IBD — Reactive arthritis often presents as a monoarthritis or oligoarthritis in large joints, such as the knees, and RA may occasionally present in this fashion as well [28]. The physical signs of both reactive arthritis and RA can be identical in the knees. (See "Reactive arthritis".)

The following findings on history, physical examination, or other assessments are more consistent with reactive arthritis than RA:

- History of recent urethritis or enteric infection
- Asymmetric pattern of joint involvement
- Symptoms or signs of enthesopathy (inflammation at the site where a tendon inserts into a bone, eg, the insertion point of the Achilles tendon into the heel)
- Keratoderma blennorrhagica or circinate balanitis (see "Reactive arthritis" and "Reactive arthritis", section on 'Extraarticular signs and symptoms')
- Radiologic evidence of sacroiliitis and/or spondylitis
- The presence of human leukocyte antigen (HLA)-B27

Involvement of the hands in reactive arthritis does not pose as great a diagnostic dilemma as that of the knees. Hand arthritis is more commonly asymmetric than in RA. Furthermore, reactive arthritis will often involve not only the joint but also the tenosynovium, entheses, and surrounding tissues of the digit, giving rise to a characteristic "sausage" swelling of the fingers (or toes if the feet are involved) (picture 1).

The arthritis associated with inflammatory bowel disease (IBD) or other gastrointestinal (GI) disorders is also part of the differential diagnosis. Patients with IBD may develop a peripheral polyarthritis with prominent involvement of the metacarpophalangeal (MCP) joints that can be mistaken for RA; other presentations include predominantly large joint oligoarticular involvement or a spondyloarthropathy with sacroiliitis. This disorder may be missed if abdominal symptoms or symptoms of diarrhea and/or blood or mucus in the stool are not prominent or are not specifically sought in the history. (See "Clinical manifestations and diagnosis of arthritis associated with inflammatory bowel disease and other gastrointestinal diseases".)

Lyme arthritis — Lyme arthritis, a late manifestation of Lyme disease, occurs primarily in individuals who live in or travel to Lyme disease-endemic areas. Lyme arthritis is characterized by intermittent or persistent inflammatory arthritis in a few large joints, especially the knee. The most commonly involved joints, after the knee, are the shoulder, ankle, elbow, temporomandibular joint, and wrist. Migratory arthralgias without frank arthritis may occur during

early localized or early disseminated Lyme disease. (See "Musculoskeletal manifestations of Lyme disease".)

The diagnosis of Lyme arthritis can usually be made by serologic testing, which should be performed in patients presenting with undiagnosed inflammatory arthritis in endemic areas. In addition, several clinical features help distinguish Lyme arthritis from RA. Unlike RA, for example, involvement of the small joints of the hands and feet is uncommon in patients with Lyme arthritis. Furthermore, many, but not all, patients with Lyme arthritis will describe an antecedent history of erythema migrans or other early disease manifestations. (See "Musculoskeletal manifestations of Lyme disease", section on 'Laboratory testing'.)

Psoriatic arthritis — Psoriatic arthritis can be difficult to distinguish from RA because a symmetric polyarthritis can be observed in both disorders [29]. We generally make the diagnosis of psoriatic arthritis in such patients who also have psoriasis and are seronegative for RF and anti-CCP. However, we diagnose RA in those with a symmetric polyarthritis who are seropositive for at least one of these antibodies, since skin psoriasis is so common. However, serologic testing and skin findings may not be informative, since patients with RA may not have RF or CCP antibodies (eg, seronegative RA) and the joint symptoms of psoriatic arthritis may precede the onset of skin disease by many years. Such patients should be evaluated and monitored for other signs more characteristic of psoriatic arthritis, such as nail changes or enthesitis; occasional patients exhibit overlapping features of both disorders.

In some patients with a symmetric inflammatory polyarthritis, the only clue to the diagnosis of psoriatic arthritis is a family history of psoriasis. However, in the majority, the findings of skin psoriasis, nail changes (onychodystrophy), sausage toes or fingers, oligoarticular asymmetric large joint or spinal involvement, and/or arthritis mutilans help distinguish the two entities. (See "Clinical manifestations and diagnosis of psoriatic arthritis".)

Polymyalgia rheumatica — Polymyalgia rheumatica (PMR) can sometimes be mistaken for RA in patients presenting with more limited arthritis over the age of 50 who are seronegative or only have a low RF titer. Unlike RA, PMR is usually associated with marked myalgias in the shoulders and hips, and joint involvement tends to be milder, more limited, and more often asymmetric.

Stiffness is thus more axial in PMR and more likely to be described as difficulty getting out of bed, while stiffness in the small joints of the hands and other involved joints predominates in RA, in which difficulty buttoning clothing is more likely to be reported. However, similar

complaints to RA may be present in patients with PMR with synovitis affecting the small joints in the hands.

The arthritis in PMR tends to respond strikingly to modest doses of glucocorticoids used to control other symptoms [30]. In patients initially diagnosed with PMR, persistent or recurrent small joint arthritis with tapering of glucocorticoids and the absence of other findings suggestive of PMR may lead to a change in the diagnosis to RA after several months or even years of treatment. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica".)

Crystalline arthritis — Crystalline arthritis (gout and pseudogout) can become chronic and even assume a polyarticular distribution. The diagnosis is established by the finding of urate or calcium pyrophosphate crystals, respectively, in synovial fluids. The presence of tophi on physical examination, the detection of serological markers of RA, and the characteristic appearance of gouty erosions are also useful in distinguishing RA from polyarticular gout. (See "Clinical manifestations and diagnosis of gout" and "Clinical manifestations and diagnosis of calcium pyrophosphate crystal deposition (CPPD) disease".)

Infectious arthritis — Infectious arthritis is usually monoarticular, but polyarthritis can occur. The diagnosis is established by culturing the pathogen from the synovial fluid or from the blood. Patients with septic arthritis may or may not appear toxic on examination, depending upon the stage of their infection, the presence of medications that can mask infection (eg, glucocorticoids), and other clinical variables. Peripheral blood leukocytosis with a left shift is common but not invariably present.

A low threshold for suspecting infection is required, particularly in compromised hosts. Patients with RA are at increased risk for joint infections because a damaged joint can serve as a nidus of infection. Synovial fluid changes, including marked granulocytosis and low glucose levels, are similar to those seen in RA. (See "Septic arthritis in adults".)

Osteoarthritis — Osteoarthritis (OA) can be confused with RA in the middle aged or older patient when the small joints of the hands are involved. However, different patterns of clinical involvement usually permit the correct diagnosis (table 3). The following are examples (see "Clinical manifestations and diagnosis of osteoarthritis"):

- OA of the fingers typically affects the distal interphalangeal joints and is frequently associated with Heberden's nodes in this area. In contrast, RA typically affects the MCP and proximal interphalangeal (PIP) joints and is not associated with Heberden's nodes.

- The carpometacarpal joint of the thumb is typically involved in OA.
- Swelling of the joints is hard and bony in OA. In contrast, soft, warm, boggy, and tender joints are typical of RA.
- Stiffness of the joint is a very common feature of RA but is relatively uncommon in OA. Furthermore, the stiffness of RA is characteristically worse after resting the joint (eg, morning stiffness), while the stiffness of OA, if present, is typically worse after any effort and is often described as evening stiffness. Morning stiffness in OA, when present, is usually transient or lasts no more than a few minutes, unlike the more sustained stiffness typical of RA.
- Radiographs also help distinguish RA from OA. OA is characterized by narrowing of the joint space due to cartilage loss and osteophytes due to bone remodeling, but not erosions or cysts.
- OA is classically associated with the absence of RFs and normal levels of acute phase reactants. However, RFs may be present, usually in low titer, consistent with the patient's (older) age.

Paraneoplastic disease — Joint pain or frank polyarthritis can occur in association with cancer. The following are some examples:

- Hypertrophic osteoarthropathy – Patients with hypertrophic osteoarthropathy, sometimes termed hypertrophic pulmonary osteoarthropathy, typically demonstrate clubbing of the digits, joint pain, and periosteal new bone formation. Additionally, they give a characteristic history suggestive of bone pain and often describe the pain as deep and achy; nocturnal pain is common. Joint effusions may occur. This is an important diagnosis because lung cancer is the commonest underlying cause. (See "Malignancy and rheumatic disorders", section on 'Hypertrophic osteoarthropathy'.)
- Myelodysplasia – Patients with myelodysplastic syndrome sometimes develop an inflammatory polyarthritis that mimics RA [31]. The majority of patients are seronegative for RF and few are positive for anti-citrullinated peptide antibody or exhibit erosive changes on joint radiography. The arthritis may precede the diagnosis of myelodysplasia in at least half of the patients. In a cohort study of 87 patients with myelodysplastic syndrome, five (6 percent) had inflammatory arthritis that resembled RA [32]. Persistence of anemia, other cytopenias, or elevated acute phase reactants despite control of the arthritis should

heighten suspicion of myelodysplasia [31]. (See "Clinical manifestations and diagnosis of the myelodysplastic syndromes".)

Multicentric reticulohistiocytosis — Multicentric reticulohistiocytosis is a rare but highly destructive form of arthritis. The rapid joint destruction of multicentric reticulohistiocytosis resembles the arthritis mutilans occasionally observed in RA. Multiple smooth, shiny, erythematous nodules located in the periungual region suggest multicentric reticulohistiocytosis. Binucleated or multinucleated foreign body type giant cells are present on skin or synovial biopsies in multicentric reticulohistiocytosis [33,34]. In a minority of patients, an underlying malignancy may be present. (See "Cutaneous manifestations of internal malignancy", section on 'Summary'.)

Multicentric reticulohistiocytosis is relatively resistant to glucocorticoids and to disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and hydroxychloroquine. However, there are case reports of response to tumor necrosis factor (TNF)-alpha inhibition [35,36] and to parenteral administration of an aminobisphosphonate [37,38].

Sarcoid arthropathy — Chronic arthritis in sarcoidosis may be oligoarticular or polyarticular and can appear similar to RA in some patients. It most frequently affects the ankles, knees, hands, wrist, and MCP and PIP joints, and it is frequently associated with parenchymal pulmonary disease.

This disorder is distinguished from RA by the following findings:

- Elevated serum concentrations of angiotensin-converting enzyme (ACE) are found in up to 50 percent of patients.
- A chest radiograph may reveal characteristic findings of sarcoidosis.
- The pattern of acute arthritis with Lofgren's syndrome in patients with sarcoidosis is not observed in those with RA.

(See "Sarcoid arthropathy".)

Fibroblastic rheumatism — Fibroblastic rheumatism, a rare disease of unknown etiology, shares the features of arthralgia, arthritis, and nodules with RA [39-41]. Flexion contractures of the fingers occur in most patients, while thickened palmar fascia is noted in about one-half of reported cases. Biopsy of a nodule or thickened skin typically reveals increased thickness of collagen fibers and fibroblastic proliferation. Decreased elastic fibers and the presence of myofibroblasts are noted in approximately 50 percent. Radiographic findings are variable, but

periarticular osteopenia and erosions may be noted.

Due to the rarity of fibroblastic rheumatism, there is no well-established treatment. Progressive disease may lead to sclerodactyly and ankylosis of affected joints.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Rheumatoid arthritis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Rheumatoid arthritis (The Basics)")
- Beyond the Basics topics (see "Patient education: Rheumatoid arthritis symptoms and diagnosis (Beyond the Basics)" and "Patient education: Rheumatoid arthritis treatment (Beyond the Basics)" and "Patient education: Complementary and alternative therapies for rheumatoid arthritis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Rheumatoid arthritis (RA) should be suspected in the adult patient who presents with

inflammatory polyarthritis. The initial evaluation of such patients requires a careful history and physical examination, along with selected laboratory testing to identify features that are characteristic of RA or that suggest an alternative diagnosis. (See 'Evaluation for suspected RA' above and 'Differential diagnosis' above.)

- The following components of the medical evaluation are helpful in making a clinical diagnosis of RA, both for the identification of characteristic findings and for the exclusion of other diagnoses (see 'Evaluation for suspected RA' above):
  - A thorough medical history, with particular attention to joint pain, stiffness, and associated functional difficulties
  - A complete physical examination to assess for synovitis, limited joint motion, extraarticular disease manifestations, and signs of diseases included in differential diagnosis
  - Basic and selected laboratory testing, including assays for acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibodies, and antinuclear antibodies (ANA)
  - Selected imaging studies, including bilateral radiographs of the hands, wrists, and feet
  - Arthrocentesis, if there is diagnostic uncertainty
- The diagnosis of RA can be made in a patient with inflammatory arthritis involving three or more joints, positive RF and/or anti-citrullinated peptide/protein antibody, disease duration of more than six weeks, and elevated CRP or ESR, but without evidence of diseases with similar clinical features. (See 'Our diagnostic criteria' above.)
- RA may also be diagnosed in patients without all of the classic findings of disease. This includes patients with seronegative RA, those with clinically quiescent disease, and those with recent onset RA. Such patients have findings/clinical features that are generally consistent with those described as meeting the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. (See 'Patients not meeting above criteria' above.)
- The 2010 classification criteria for RA were developed primarily for the identification for

research purposes of patients with RA who are at high risk of persistent symptoms and joint injury unless treated with disease-modifying antirheumatic drugs (DMARDs). These criteria have replaced the 1987 criteria, which were based only upon patients with established disease. (See 'Classification criteria' above.)

- The differential diagnosis of RA includes multiple disorders that can generally be distinguished clinically or by limited laboratory testing, based upon a combination of the following features (see 'Differential diagnosis' above):
  - Limited duration (eg, in viral arthropathy)
  - The presence of other diseases (eg, in psoriatic arthritis or arthritis of inflammatory bowel disease [IBD])
  - The pattern of joint involvement and other symptoms (eg, in psoriatic arthritis, spondyloarthropathy, or polymyalgia rheumatica [PMR])
  - The presence of systemic features (eg, in systemic lupus erythematosus [SLE] or dermatomyositis [DM])
  - Diagnostic laboratory tests associated with other conditions (eg, specific autoantibodies in SLE, synovial fluid crystals in gout or calcium pyrophosphate disease)
  - Relatively high specificity of anti-CCP antibodies for RA

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Topic 7504 Version 20.0

GRAPHICS

1987 American College of Rheumatology (formerly American Rheumatism Association) revised classification criteria for rheumatoid arthritis

Criterion	Description
Morning stiffness	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.
Arthritis of three or more joint areas	At least three joint areas (out of 14 possible areas; right or left PIP, MCP, wrist, elbow, knee, ankle, MTP joints) simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) as observed by a physician.
Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.
Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs, without absolute symmetry is acceptable).
Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions as observed by a physician.
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5 percent of normal control subjects.
Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand or wrist radiographs, which must include erosions or unequivocal bony decalcification localised in, or most marked adjacent to, the involved joints (osteoarthritis changes alone do not qualify).

Note: For classification purposes, a patient has RA if at least four of these criteria are satisfied (the first four must have been present for at least six weeks).

Graphic 71659 Version 5.0

Confirming a diagnosis of rheumatoid arthritis (RA)*: Differential diagnosis

Diagnosis	Sex	Age	Lab tests	Comments
Undifferentiated seronegative polyarthritis	F > M	35-65	10-15 percent RF+	Chronic seronegative inflammatory polyarthritis, atypical of RA or fails to meet classification criteria for RA. Up to 20 percent of cases may evolve into RA; nearly 50 percent will go into remission.
Psoriatic arthritis	M = F	30-55	<20 percent RF+	10 percent of those with psoriatic arthritis will have an RA-like distribution (MCPs, PIPs, wrists). Cutaneous psoriasis will be evident in the vast majority of cases.
Tophaceous gout	M > F	25-70 M	95 percent RF–	Intermittent inflammatory arthritis during the onset, with evolution of tophi and chronic inflammatory polyarthritis. Elevated serum urate and tophi help distiguish from RA.
	F	>45	>95 percent ↑ serum urate	
Erosive inflammatory OA	F > M	>60	RF– (or normal for age)	Chronic polyarthritis with intermittent or sustained inflammation affecting PIP and DIP joints. Radiographs demonstrate distinctive erosions and evidence of OA.
Pseudogout	F = M	>60	5-10 percent RF+	5 percent of patients will have "rheumatoid-like" inflammatory arthritis with stiffness, fatigue, synovitis, and elevated ESR, often lasting four weeks to several months.
Reactive arthritis (formerly known as Reiter's syndrome)	M > F	16-50	95 percent RF–; 50-80 percent HLA-B27+	See criteria for spondyloarthropathies; often associated with low back pain, ocular, genitourinary, or GI symptomatology and enthesitis (heel pain).
Enteropathic arthritis	M = F	All ages	95 percent RF–	20 percent of patients with Crohn's disease or ulcerative colitis will develop peripheral arthritis. Diagnosis may be difficult until GI involvment becomes apparent. Associated with oral ulcerations, GI symptoms or other features of spondyloarthropathy.
Systemic lupus erythematosus	F > M	15-40	10-15 percent RF+; usually ANA+	Chronic nondeforming inflammatory polyarthritis associated with ANA positivity and other features of SLE.
Polymyositis/ dermatomyositis	F > M	30-60	95 percent RF–; 50 percent ANA+; 70 percent ↑ CK	Chronic inflammatory arthritis uncommonly occurs early in course of PM/DM. Features of proximal muscle weakness, bulbar dysphagia, muscle enzyme elevation, or skin involvement (ie, Gottron's papules) should be sought.
Scleroderma	F > M	30-50	95 percent RF–; >90	Chronic inflammatory polyarthritis may predominate over skin changes early in the disease. Associated

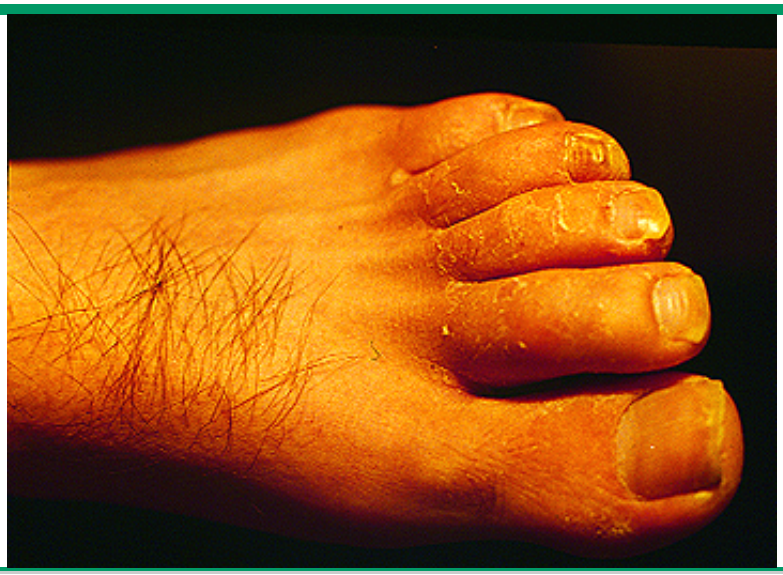
			percent ANA+	with Raynaud's phenomenon, sclerodactyly, dysphagia, hypertension, or renal abnormalities.
Sarcoid arthritis	F > M	20-40	25 percent RF+	15 percent of patients with sarcoidosis will develop arthritis. Early in the disease a chronic inflammatory oligo or polyarthritis lasting weeks to months may develop and typically involve the ankles and knees. Other features of sarcoidosis (ie, erythema nodosum, hilar adenopathy) are usually apparent.
Parvovirus B19-associated arthritis	F > M	Any age	<10 percent RF+; >80 percent anti-B19 IgM antibodies (acutely)	Adults manifest a flu-like picture, seldom develop the "slapped-cheek" rash; arthralgias are more common than arthritis. Arthritis is an acute inflammatory polyarthritis with an RA-like distribution lasting two weeks. Less than 10 percent develop a chronic inflammatory arthritis.
Polymyalgia rheumatica	F > M	>50	90 percent RF–; >95 percent ↑↑ ESR	Proximal girdle pain and stiffness without synovitis.

ANA: antinuclear antibody; DIP: distal interphalangeal; DM: dermatomyositis; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; MCP: metacarpophalangeal; OA: osteoarthritis; PIP: proximal interphalangeal; PM: polymyositis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.
* 1. RA often begins insidiously with vague constitutional and musculoskeletal symptoms that may last for weeks or months before synovitis becomes apparent.
2. During the first six months of RA, <50 percent of patients will be RF-positive, and the sensitivity of the 1987 ACR criteria is reduced.
3. A variety of less common chronic inflammatory seronegative articular conditions may clinically resemble early RA. It may be necessary to observe and evaluate the patient repeatedly for evolution of the disorder and manifestation of features that will distinguish them from RA. The above disorders can mimic RA.

Data from: Lipsky P. Algorithms for the diagnosis and management of musculoskeletal complaints: A new tool for the primary-care provider. (See www.swmed.edu/home_pages/cme/endurmat/lipsky/index.html.)

Graphic 52176 Version 5.0

Sausage toe in reactive arthritis



Sausage toe (with diffuse swelling) of the second digit and mild keratoderma blenorrhagica on the dorsum of the foot in a man with reactive arthritis (formerly Reiter's syndrome).

Courtesy of Craig Wiesenhutter, MD and David Yu, MD.

Graphic 61696 Version 1.0

Clinical distinction between rheumatoid arthritis and osteoarthritis

Feature	Rheumatoid arthritis	Osteoarthritis
Primary joints affected	Metacarpophalangeal	Distal interphalangeal
	Proximal interphalangeal	Carpometacarpal
Heberden's nodes	Absent	Frequently present
Joint characteristics	Soft, warm, and tender	Hard and bony
Stiffness	Worse after resting (eg, morning stiffness)	If present, worse after effort, may be described as evening stiffness
Laboratory findings	Positive rheumatoid factor	Rheumatoid factor-negative
	Positive anti-CCP antibody	Anti-CCP antibody-negative
	Elevated ESR and CRP	Normal ESR and CRP

CCP: cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Graphic 57005 Version 5.0

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