Educational Objectives:

1. Recognize the typical clinical presentation of rheumatoid arthritis in the primary care setting
2. Describe the usefulness and limitations of available laboratory data to support the diagnosis of rheumatoid arthritis
3. Review when to refer a patient with rheumatoid arthritis to a specialist
4. Appropriately monitor patients treated with DMARDS or biologic agents for rheumatoid arthritis

CASE ONE:

Mr. CR is a 57-year-old man who presents to your clinic for evaluation of joint and muscle pain. He reports having aching in both legs extending into his feet for the past month and states that, “I feel like I was hit by a truck.” He had been previously active but has had to limit his typical walking routine due to discomfort in both legs. He reports that most of the discomfort is in his hips, but over the past few weeks he also has noticed some pain in both feet. When he developed the foot pain he also noticed the same discomfort occurring in both shoulders, which has been limiting his ability to raise his arms overhead. He reports having difficulty getting out of bed and requires more than 30 minutes to get moving in the morning. He has tried over the counter ibuprofen with minimal improvement of his discomfort. On physical examination, Mr. CR appears uncomfortable and in mild distress; he is able to walk in from the waiting room but at a slow pace. His vital signs are within normal limits. On joint examination, there is pain in both shoulders with passive abduction past 120 degrees and with resisted internal and external rotation. There is diffuse tenderness of the shoulders and lateral hips, but with a normal hip range of motion. There is no obvious joint swelling on examination including the joints of the hands and feet.
Questions:

1. What is the differential diagnosis of your patient’s pain at this point? How do you distinguish between arthritis and arthralgia? What else would you ask Mr. CR? Is there any testing that would be helpful at this point?

The differential diagnosis of the patient’s pain at this point is broad. One of the first steps is to try to distinguish true joint arthritis from arthralgia. Arthritis is a sign that indicates inflammation of a joint, while arthralgia is a symptom which refers to aching in a joint or the tissues around the joint. Arthralgia can accompany arthritis but can also be a result of trauma or internal joint derangements. True joint inflammation can begin as arthralgia and progress to arthritis over time. It is important to emphasize that the differential in an initial rheumatologic presentation must remain broad and that time and repeated examinations will often lead to a clearer diagnosis.

Typically, arthritis on physical examination has findings consistent with inflammation, including rubor (redness), dolor (pain), calor (heat), tumor (swelling), and functio laesa (loss of function). In addition, morning stiffness lasting more than one hour tends to occur more commonly with true inflammatory arthritis, and not arthralgia. Arthralgia certainly has overlap with arthritis, but tends to lack some of the cardinal features, including redness, swelling, and warmth. This important distinction guides further work-up and treatment, as anti-inflammatory medications and early treatment with disease modifying anti-rheumatic drugs (DMARDs) are essential in the management of inflammatory arthritides.

If you diagnose an inflammatory arthritis, it is essential to document the distribution and overall pattern of joint involvement. Though there is overlap, inflammatory monoarticular arthritis often occurs with crystal-associated arthritis or infection, while most other inflammatory arthritides present with oligoarticular or polyarticular involvement. This patient is presenting with bilateral shoulder and hip pain and morning stiffness, indicating a polyarticular process, though not definitively arthritis, on presentation.

At this time, Mr. CR has bilateral shoulder and hip pain and stiffness with evidence for either arthritis or arthralgias in these joints. The differential diagnosis is very broad and includes an early presentation of an inflammatory arthritis (rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, psoriatic arthritis, hemochromatosis, reactive arthritis secondary to inflammatory bowel disease, scleroderma, Still’s disease), a post-viral polyarthritis, alphavirus infection (if recent travel), polynyalgia rheumatica, or a non-
inflammatory condition such as osteoarthritis or fibromyalgia. Further testing that could be considered at this point can help to narrow this differential diagnosis and includes:

- Lab testing – Testing with ESR or CRP could be helpful early on to guide if the condition is inflammatory or not.
- Imaging – X-rays of involved joints could be helpful if there is evidence for joint erosions, which would favor an inflammatory arthritis. If joint erosions are present, this typically indicates that the disease process has been more long-standing, as erosions tend to occur after months of inflammation.

A family history of inflammatory arthritis can also be helpful in this situation as many autoimmune inflammatory arthritides tend to run in families, and can help to narrow the differential diagnosis. Social history is also important as both current and past cigarette use are associated with rheumatoid arthritis. In a study of twins discordant for rheumatoid arthritis, there was a strong association with smoking, with an odds ratio of 3.7 for smokers being diagnosed with rheumatoid arthritis (Silman, 1996).

CASE ONE CONTINUED:

Mr. CR does not have any known past medical history and does not take any medications other than ibuprofen recently. He denies any recent travel and does not recall a family history of rheumatoid arthritis, lupus, or any other known arthritis. He previously smoked one to two packs per day for 20 years but quit 18 years ago. X-rays of the shoulders and hips are unremarkable without evidence for joint erosion. Laboratory testing reveals an ESR of 82 mm/hr and CRP (inflammation) of 42 mg/L. You strongly consider the diagnosis of polymyalgia rheumatica (PMR) and start Mr. CR on prednisone 20 mg daily. A few days after starting prednisone, Mr. CR feels dramatically improved and is able to resume his normal activities.

One month later, after tapering prednisone to 10 mg daily, he presents to you with complaints of recurrent hip and shoulder pain, as well as pain and stiffness in both hands. He has been miserable in the mornings, reporting great difficulty in getting out of bed and starting his day. It takes Mr. CR almost 1.5 hours to get moving in the mornings and he reports that his hands are so uncomfortable in the mornings that he cannot even shave. Joint examination of his hands reveals bilateral synovial thickening and joint swelling in both wrists, as well as his second and third metacarpophalangeal joints.
2. How do you explain Mr. CR’s current presentation? What is your differential diagnosis at this point?

Mr. CR initially presented with bilateral shoulder and hip discomfort with a dramatic improvement after starting prednisone. This presentation and response to treatment is very consistent with an initial diagnosis of polymyalgia rheumatica (PMR). However, the onset of new symptoms with tapering suggests that another diagnosis might be affecting Mr. CR. In a prospective study of 116 patients who presented with bilateral girdle pain for more than one month with an elevated ESR, almost 20% were ultimately diagnosed with rheumatoid arthritis (Caporali, 2001). Thus, it is important to emphasize that rheumatologic diseases may evolve over time and the diagnosis is not always apparent on initial presentation.

At this point, there is evidence on physical examination for joint inflammation in the hands and wrists, with both synovial thickening and joint swelling. The differential diagnosis for this patient’s presentation includes the following:

(Disease state-typical signs/symptoms)
- SLE (systemic lupus erythematosus) – malar/discoid rash, photosensitivity, oral ulcers
- Viral polyarthritis – recent viral infection/prodrome, symptoms less than six weeks, recent travel
- Rheumatoid arthritis – symmetric involvement, hands and wrists involved
- Sarcoidosis – shortness of breath, dry cough
- Psoriasis – prior or current psoriatic skin lesions, nail changes including pitting and onycholysis
- Reactive arthritis – conjunctivitis, urethritis, back pain
- Inflammatory bowel disease – diarrhea, weight loss, abdominal pain
- Scleroderma – skin tightness, reflux symptoms, pulmonary involvement
- Gout – previous history of gout
- Hemochromatosis – bronze skin, diabetes, second and third MCP involvement

Infections can also be considered. Recent travel to countries where Chikungunya is endemic should also be assessed. This mosquito-borne alphavirus infection causes an acute viral syndrome with high fevers and myalgias but can also lead to bilateral joint arthritis which can last for up to six months after the onset of infection. It can be difficult to differentiate from rheumatoid arthritis but resolves without treatment in most patients. Hepatitis C can cause arthralgias but also can cause arthritis. One type is associated with cryoglobulinemia and involves medium and large joints. The most common form (two-thirds of cases) resembles rheumatoid arthritis, but can be distinguished by serology (Sanzzone, 2006).
3. **How do you make the diagnosis of rheumatoid arthritis? What further testing is indicated?**

The diagnosis of rheumatoid arthritis requires both clinical and laboratory findings. For many years, this diagnosis was based on the American College of Rheumatology (ACR) criteria from 1987. Most of the clinical trials for medications used to treat rheumatoid arthritis from 1987 – 2010 used the 1987 ACR criteria for selection of patients. The presence of four of the following seven criteria is considered diagnostic for rheumatoid arthritis:

- Morning stiffness for more than one hour (duration for more than six weeks)
- Arthritis of three or more joint areas (for more than six weeks)
- Arthritis involving the hands (for more than six weeks)
- Symmetric arthritis (for more than six weeks)
- Rheumatoid nodules (subcutaneous, usually nontender nodules typically occurring in areas of repetitive trauma, including the elbows)
- Presence of rheumatoid factor (RF)
- X-ray changes with erosions

These criteria can still be used to diagnose rheumatoid arthritis, though they have their limitations. Four of the seven criteria require symptoms for more than six weeks, and two of the criteria are usually only present in long-standing rheumatoid arthritis (rheumatoid nodules and erosive changes on x-ray). Therefore, the 1987 ACR criteria have lower sensitivity for early disease presentation, which limit their usefulness in helping to identify patients who should be treated early with DMARDs. The overall sensitivity and specificity of these criteria for early RA (less than one year) are 77% and 77%, but for established RA (more than one year) are 79% and 90%, respectively (Banal, 2009).

In addition to the limitations of the 1987 criteria for diagnosing early RA, the criteria also do not take into account advances in laboratory testing for anti-cyclic citrullinated peptide (anti-CCP). Because of these issues, in 2010, ACR and the European League Against Rheumatism (EULAR) developed revised diagnostic criteria to allow for earlier diagnosis of rheumatoid arthritis (Aletaha, 2010). These criteria can be applied to patients with at least one joint with definite clinical synovitis or swelling and without another diagnosis that is more likely to explain the patient’s symptoms. If a patient has a score of ≥6, the patient can be classified as having definite rheumatoid arthritis, per the EULAR criteria (see below). Data from the Nurses’ Health Study indicate a sensitivity and specificity for the EULAR criteria of 79% and 87% respectively (Kasturi, 2014).
The following are the EULAR criteria:

1) Joint involvement
   a. One large joint (shoulders, elbows, hips, knees, ankles) – 0 pts
   b. 2-10 large joints – 1 pt
   c. 1-3 small joints (+/- large joints) – 2 pts
   d. 4-10 small joints (+/- large joints) – 3 pts
   e. More than 10 joints (at least one small joint) – 5 pts

2) Serology
   a. RF and anti-CCP both negative – 0 pts
   b. Low positive RF or low positive anti-CCP – 2 pts
   c. High positive RF or high positive anti-CCP – 3 pts

3) Acute phase reactants
   a. Normal CRP and normal ESR – 0 pts
   b. Abnormal CRP or abnormal ESR – 1 pt

4) Duration of symptoms
   a. Less than 6 weeks – 0 pts
   b. ≥6 weeks – 1 pt

In order to apply the 2010 ACR/EULAR criteria, you should test Mr. CR for RF and anti-CCP, as well as repeating an ESR and CRP. These laboratory tests not only aid in the diagnosis of RA but can also be used to follow disease progression and response to treatment. In addition to these laboratory tests, x-rays of any involved joints should be taken to evaluate for erosive changes, which could support the diagnosis of long-standing RA.

Elevation of inflammatory markers (CRP and/or ESR) can be supportive of the diagnosis of an inflammatory condition but are very nonspecific. On the other hand, the absence of elevated inflammatory markers would argue against significant active inflammation. Similarly, a positive RF can support the diagnosis of RA. However, both false positives and false negatives occur in patients with RA. The sensitivity of a positive RF for the diagnosis of RA is about 70%, with a specificity of 85% (Nishimura, 2007). False-positive RFs are known to occur in a variety of other inflammatory conditions and are
also associated with advancing age. The following are commonly associated with the presence of a positive RF (Shmerling, 2017):

- Other rheumatic diseases:
  - Sjögren’s syndrome - 75-95%
  - Mixed connective tissue disease - 50-60%
  - Cryoglobulinemia - 40-100%
  - SLE - 15-35%
  - Polymyositis/Dermatomyositis - 5-10%
  - Sarcoidosis - up to 33%

- Non-rheumatic causes:
  - Chronic infections (especially hepatitis B and C): As noted above, hepatitis C can be associated with its own arthritis, can have a positive RF, but will be negative for anti-CCP.
  - Malignancy - 5-25%
  - Age >60 years - up to 25% of elderly

Given the poor specificity of ESR, CRP, and RF, an anti-citrullinated peptide antibody (anti-CCP) should also be sent. The presence of anti-CCP strongly supports the diagnosis of rheumatoid arthritis given its high specificity. Anti-CCP levels are also useful in diagnosing RA in the early stages of disease. The specificity of a positive anti-CCP is 95% (compared with 85% for RF), though the sensitivity is only 67% (Nishimura, 2007).

**CASE ONE CONTINUED:**

Lab tests reveal an ESR of 72 mm/h, CRP of 48 mg/L, and low positive RF. A test for anti-CCP comes back elevated at 35, in the low-positive range. Hand and wrist x-rays reveal bilateral soft tissue swelling in the wrists, as well as early erosions in the bilateral second and third MCP joints, consistent with an inflammatory arthritis.

4. **Does this patient have rheumatoid arthritis? What are the options for treatment of this patient’s case?**
   Using the 1987 ACR criteria, Mr. C.R. meets two of seven criteria: positive rheumatoid factor and erosive changes on x-ray. If he had had symptoms for over six weeks, he would meet four more criteria: morning stiffness, involvement of more than three joints, hand arthritis, and symmetric arthritis. Since his current duration of symptoms is only
one month, it is unclear if he truly meets the diagnosis of RA using the 1987 ACR criteria.

Using the 2010 EULAR criteria, Mr. C.R. meets the following criteria:

- Four to 10 small joints = 3 points (bilateral 2\textsuperscript{nd} and 3\textsuperscript{rd} MCP joints = 4 joints)
- Low positive RF and anti-CCP = 2 points
- Abnormal ESR and CRP = 1 point
- Symptoms <6 weeks = 0 points

With a total EULAR score of 6 points, Mr. CR can be classified as having definite RA.

Though NSAIDS or corticosteroids might provide temporary improvement of symptoms and pain control, they are not considered to be first-line treatment in rheumatoid arthritis. The American College of Rheumatology (2015 guidelines) recommends early treatment with a DMARD to prevent joint destruction and to slow disease progression in all patients with symptomatic rheumatoid arthritis of any severity (Singh, 2015). Unless there is a clear contraindication, for all patients with early RA (defined as less than six months), regardless of the severity of symptoms, the current guidelines recommend initiation of methotrexate as first-line DMARD monotherapy, as it is usually well tolerated and effective as monotherapy. If needed for symptom control, short courses of prednisone or an NSAID can be used simultaneously. Other DMARDs that can be used if there is a contraindication to methotrexate (such as chronic liver disease, pregnancy, breastfeeding, blood dyscrasias) are hydroxychloroquine, leflunomide, and sulfasalazine. The goal of treatment is for disease remission or at least a 50% reduction in disease activity at three months. Disease activity can be assessed using the Disease Activity Score derivative for 28 joints (DAS28), Simplified Disease Activity Index (SDAI), or Clinical Disease Activity Index (CDAI), all of which are available online. If patients continue to have symptoms on methotrexate, there is no preference for the next DMARD to be added. Any of the above agents can be added to methotrexate. Biological agents, including TNF inhibitors (etanercept, infliximab, adalimumab), are added for continued disease progression/activity with methotrexate treatment. Other classes of biologic agents include anti B-cell (rituximab), anti T-cell co-stimulation (abatacept), and anti-IL 6R (tocilizumab). In order to begin early treatment with a DMARD to prevent joint destruction, this patient should be referred to a rheumatologist early on in the disease course.

5. **What parameters need to be followed by you as his primary care physician prior to and while undergoing treatment for rheumatoid arthritis?**

Preceptors should review the periodic monitoring needed for the commonly prescribed DMARDs, in addition to baseline chemistries and liver function tests.
• Methotrexate and leflunomide – screening for hepatitis B and C since these medications are contraindicated in chronic liver disease; baseline age-appropriate vaccinations; CBC and LFTs every two to four weeks at initiation and with dose changes for three months (then can check every three months); monitor for potential pulmonary toxicity by symptom assessment (new cough, dyspnea)

• Hydroxychloroquine – complete eye examination within one year of initiation given the risk of irreversible retinopathy. Low risk patients (less than 60 years old, normal liver function, no prior retinal disease) do not require further eye exams for five years. Patients with risk factors require annual eye examinations.

• Sulfasalazine – baseline age-appropriate vaccinations; CBC and LFTs every two to four weeks after initiation and with dose changes for three months (then can check every three months)

Patients who are candidates for anti-TNF therapy need to be screened for latent tuberculosis because treatment can cause reactivation. If a patient has latent TB, at least one month of treatment for latent TB is required prior to initiating anti-TNF therapy. In addition, biologic therapy with anti-TNF agents is contraindicated in patients with class III or IV congestive heart failure with an ejection fraction ≤50%, and in those with untreated chronic hepatitis B or treated hepatitis B with Child-Pugh class B cirrhosis or higher. Patients with chronic hepatitis C can be treated with etanercept.

Finally, for all patients who will be receiving either a DMARD or biologic agent, it is recommended that they be vaccinated (or confirmed up to date) for influenza, pneumococcus (both pneumovax 23 and Prevnar 13), hepatitis B, human papillomavirus, and herpes zoster. While a patient is on a DMARD, all vaccinations (except those that are live-attenuated) can be given if needed for routine health maintenance.
CASE ONE CONTINUED:

Mr. CR is seen by rheumatology and initiated on weekly methotrexate. He returns for routine follow-up with you every three months for the next six months and has had almost complete resolution of hand and wrist pain, as well as shoulder and hip pain. However, after six to seven months of good control on weekly methotrexate, he develops recurrent joint pains in the hands and wrists despite titration of methotrexate to 20 mg weekly, as well as the stepwise addition of sulfasalazine and hydroxychloroquine. He now takes methotrexate, sulfasalazine, and hydroxychloroquine and feels miserable.

Mr. CR presents for follow-up with you and appears uncomfortable and fatigued. His physical examination reveals bilateral warmth and swelling of the wrists and multiple MCP and PIP joints. He reports that his rheumatologist wants to start him on stronger, biologic therapy, and he asks your opinion.

6. What screening test is necessary to consider biologic therapy for Mr. CR? How do you interpret the results and how does this affect your management?

Though the overall risk is low, all patients who are being considered for biologic therapy with anti-TNF agents need to be screened for latent tuberculosis (TB). This is best done with either a tuberculin skin test (PPD) or interferon gamma release assay (IGRA). If the testing is negative, then it is safe to start biologic therapy. If the screening test is positive, then the patient will need a chest radiograph to assess for the presence of active TB. If there is an infiltrate on CXR, then further testing of the sputum for acid fast bacilli will be required. If the CXR is clear, then the patient can be diagnosed with latent TB. Per the ACR 2015 guidelines, at least one month of treatment for latent TB is required prior to the initiation of biologic therapy.
Primary Reference:


Additional References:

Jeffrey Kravetz graduated from New York University School of Medicine in 1998 and completed residency in internal medicine at Yale-New Haven Hospital in 2001. Since 2001, Dr. Kravetz has been working in primary care at the West Haven VAMC and has been actively involved in teaching Yale residents in clinics and on the medical wards. Dr. Kravetz has an interest in preoperative medicine and currently runs the medical consultative service at the West Haven VAMC. His ongoing projects involve outpatient hypertension management, as well as preventive health care.
Knowledge Questions:

1. A 48-year-old woman presents with difficulty walking secondary to pain, as well as stiffness in the hands for a few hours every morning. She reports that the symptoms have been present for the past four weeks causing her to miss multiple days of work. Her physical examination reveals bilateral foot edema, as well as warmth in both hands and wrists. What is the next best step in the evaluation of this patient?
   
   a. Immediate referral to rheumatology
   b. Testing for anti-CCP antibody and RF
   c. No further testing indicated
   d. Testing for ESR, CRP, and ANA

2. A 58-year-old woman with established RA, maintained on weekly methotrexate, presents with a chronic cough and worsening dyspnea on exertion over the past four months. Physical examination reveals bilateral, inspiratory crackles at the bases with an oxygen saturation of 94% on room air at rest. A chest radiograph is unremarkable. What is the next best step in evaluating the patient’s pulmonary symptoms?
   
   a. Empiric treatment with azithromycin for atypical pneumonia
   b. Bronchoscopy
   c. High resolution CT scan of the lungs
   d. Referral to pulmonary clinic

3. A 42-year-old man presents to urgent visit clinic for evaluation of bilateral knee pain. He reports having difficulty walking secondary to the pain for the past few days and is concerned he has ‘rheumatism’, due to his family history of ‘rheumatism’. He takes no medications, drinks two to four beers per day and smokes one pack per day. Physical examination reveals a swollen and warm left knee with no other significant joint abnormalities. What is the next best step in your evaluation?
   
   a. Check an ESR and CRP
   b. Check an MRI of the left knee
   c. Empiric course of corticosteroids
   d. Arthrocentesis of the left knee
Answers:

1. **b** Since the patient has joint symptoms lasting less than six weeks, the 2010 EULAR criteria should be used for diagnostic purposes. The test that is most helpful is serology for anti-CCP or RF, since if either is high positive (3 points), the patient could be diagnosed with definitive RA (3 points for 4-10 small joints) and referred for early treatment.

2. **c** Patients with suspected methotrexate pulmonary toxicity with normal CXR’s should be further evaluated with HRCT and/or pulmonary function testing.

3. **d** This is an acute case of monoarticular arthritis. The best next step in your evaluation is synovial fluid analysis.