Top 10 issues in Rheumatoid Arthritis

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Case 1

A young woman presents with an inflammatory polyarthritis. The differential diagnosis would include rheumatoid arthritis, as well as the connective tissue diseases (CTD), and in particular, systemic lupus erythematosus. The associated clinical features will help to differentiate the diagnosis. Affirmative answers to these questions makes the diagnosis of a CTD more likely and further laboratory investigation can be focused.

For a discussion, see page 114.

Case 2

A young man presents with a two-month history of inflammatory polyarthritis. The differential diagnosis would include the spondyloarthropathies and hence the associated extra-articular features should be queried.

For a discussion, see page 114.

Rheumatoid arthritis (RA) is a chronic inflammatory disease of joints resulting in joint pain, swelling, and destruction. It affects approximately 1% of the adult population. With progression of active inflammation, RA will result in joint destruction, deformity, and associated disability. Recent research has led to specific biological therapies that are now in clinical use and need to be considered in moderate and severe rheumatoid disease.

1. What is the early clinical history of RA patients?

RA, in full development, typically displays polyarticular distribution in a symmetric pattern (Table 1). However, onset can be quite variable making for an initially wide differential diagnosis.

Onset varies with respect to mode, site, and pattern. The majority of RA cases develop insidiously over weeks to months. Initial symptoms may reflect the systemic inflammatory nature of this disease with constitutional symptoms, including general fatigue, malaise, weight loss, and diffuse poorly localised musculoskeletal stiffness. It is not unusual for the initial joint involvement to be asymmetric and oligoarticular (four joints or less involved). Subtle muscular weakness may develop, especially around involved joints, due to disuse and neuroendocrine factors.

Approximately 10% to 15% of RA cases develop abruptly with an almost explosive development of polyarticular joint inflammation, often associated with significant constitutional symptoms.

Intermediate onset RA develops over weeks with a migratory and additive pattern of joint involvement. Systemic symptoms are also common. The most common joints involved in early RA are the small joints of the hand [the metacarpalphalangeal joints, proximal interphalangeal joints (PIPs)] and the wrists.

Rheumatoid Arthritis

There are other diseases which share many similarities with RA but have very different patterns on onset: palindromic rheumatism; adult onset still's disease; polyarticular/symmetric psoriatic arthritis.

In elderly individuals, there are also disease entities which probably represent variant forms of RA: maturity onset seronegative synovitis; relapsing seronegative symmetrical synovitis with pitting edema; and polymyalgia rheumatica with peripheral synovitis.

2. Extra-articular features

RA is a systemic illness which is characterised not only by joint involvement, but also widespread "extra-articular" manifestations.

During the course of illness, constitutional symptoms are common in individuals with RA. Fatigue, malaise, low-grade fever, weight loss, and general weakness are common and related to general deconditioning and inactivity. These factors are also related to circulating inflammatory mediators, including tumour necrosis factor, interleukin 1, and a multitude of other soluble mediators produced by circulating cells, including T-cells, ß-cells, macrophages, and synoviocytes.

There are certain clinical symptoms to look for in the history of a patient with possible RA (Table 1). The presentation of polyarthritis has a wide differential diagnosis. The diagnosis of all rheumatic diseases is based upon clinical presentation. Joint involvement is typical of most, whereas the associated extra-articular manifestations are how diseases are clinically differentiated (Table 2).

The emphasis on the diagnosis of RA is that it is a clinical diagnosis. Laboratory and imaging studies only help to add further evidence to the diagnostic probability of disease.

3. Common clinical findings

Patients may present with subtle findings of joint inflammation ranging from significant pain to swelling of the joints. In early inflammatory arthritis, the most common finding is restriction of range or discomfort at the end of range of the joint. It is useful to get a sense of the patient's normal joint range. So, if you put the examining joint to the end of range in both directions and the patient grimaces or says it is uncomfortable, then this suggests an inflammatory joint. When there is marked warmth or swelling of the joint, it is often not difficult to conclude there is inflammation.

4. What lab tests should I do?

RA is a clinical diagnosis based on symptoms and clinical findings, but the use of laboratory tests can be important for confirming the presence of significant inflammation (excluding other diagnoses) and, most importantly, for conducting baseline

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Table 1
American Rheumatism Association Revised Criteria for RA

Criteria	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas out of a possible 14 (PIP, MCP, wrist, elbow, knee, ankle, MTP joints).
3. Arthritis of the hand joints	At least one area swollen in a wrist, MCP, or PIP joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint (as defined in #2) on both sides of the body.
5. Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions as observed by a physician.
6. 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% of the normal control subjects.
7. Radiographic changes	Typical changes of RA on PA hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in, or most marked adjacent to, the involved joints.

For classification purposes, a patient has RA if at least 4 of these criteria are satisfied. Criteria 1 to 4 must have been present for a least 6 weeks.

PIP: proximal interphalangeal joints
MCP: metacarpophalangeal
MTP: metatarsophalangeal
RA: rheumatoid arthritis
PA: posteroanterior

blood tests before initiating treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying medications (Table 3).

5. The differential diagnosis

There are over 100 types of inflammatory arthritis and these must be considered in patients with joint pain, swelling, and stiffness. Primary osteoarthritis (PO) can sometimes be difficult to distinguish from RA, as PO often may present with more acute pain and swelling in a few joints of the hands (PIPs and distal interphalangeals). There are many types of seronegative arthritis (ankylosing spondylitis, psoriatic arthritis, reactive arthritis, and inflammatory bowel disease) that may present with joint pain and stiffness, but the joint distribution is usually different, presenting with typical back involvement and a mono-oligoarthritis that presents asymmetrically. Early in the course of inflammatory arthritis, systemic lupus erythematosus (SLE) needs to be considered. Patients

Case 1 Discussion

Extra-articular Manifestations in Connective Tissue Diseases

Photosensitive rash
Mouth sores
Alopecia
Raynaud's phenomenon
Previous pleuro-pericarditis
History of kidney disease
Clotting diathesis
Recurrent pregnancy losses
Family history of CTD

Case 2 Discussion

Extra-articular Manifestations in Spondyloarthropathies

History of inflammatory back pain
Ocular inflammation
Gastrointestinal symptoms indicating infection or inflammation
Genitourinary symptoms indicating infection or inflammation
Mouth ulcers
Enthesopathy – heel pain, Achilles insertion pain
Chest wall pain – chostochondritis
Family / personal history of psoriasis
Family / personal history of inflammatory bowel disease
Family history of spondyloarthropathies

often present with extra-articular manifestations with lupus (rash, photosensitivity, alopecia, serositis). If SLE is suspected, an antinuclear antibody (ANA) is usually sufficient to exclude this diagnosis (ANA is 99% sensitive). If the presentation appears to be RA and an ANA is positive, it is sometimes difficult to decide which disease they may have. Over time, these patients require observation for further symptoms of SLE. Viral illness may often be associated with an acute inflammatory arthritis. The American College of Rheumatology criteria for RA suggests that the symptoms should be present for at least six weeks prior to a diagnosis of RA.

In clinical practice, this time frame may be misleading because there are many patients with an acute inflammatory arthritis secondary to viral illness that may last for several months before completely resolving. There are several other types of connective tissue disease that may present with an inflammatory arthritis, including polymyositis and systemic scleroderma. Systemic vasculitis, although much rarer, may also present with a symmetric large and small joint inflammatory arthritis. Lastly, patients may present with soft tissue rheumatism or fibromyalgia and early on it can be very difficult to decide whether they have a low grade inflammatory arthritis in keeping with early rheumatoid disease or soft tissue rheumatism. Laboratory tests, including markers of inflammation (erythrocyte sedimentation rate, C-reactive protein) and ongoing close followup, would exclude the possibility of an emergent inflammatory arthritis.

6. Should I do radiographs on suspected RA patients?

Early in the course of inflammatory arthritis, plain radiographs are not useful other than to confirm the presence of soft tissue swelling, which should be evident on clinical examination. Joint space narrowing and erosions, which are typically seen in RA, are usually not present for a number of months in established rheumatoid disease.

Prior to initiation of disease-modifying medications, baseline hand and foot radiographs should be considered. Simple posteroanterior views usually

Table 2
Extra-articular Manifestations of RA

Manifestation	Clinical Symptom/Sign
Vasculitis	Rash, mononeuritis multiplex
Subcutaneous nodules	Extensor and bony surfaces
Interstitial pulmonary fibrosis	Cough, fever, shortness of breath
Pericarditis	Sharp pain, increased in supine position, palpitation
Sjogren's syndrome	Dryness, irritability of the oral and ocular mucosae
Felty's syndrome	Hepatomegaly, splenomegaly
Ocular inflammation	Pain, irritation, reduced acuity

are adequate, although the addition of oblique views will be more sensitive in detecting some early erosions. In more longstanding RA, plain radiographs of joints will determine the presence of advanced joint space narrowing and erosions to account for joint symptoms versus residual joint inflammation to account for the patient's symptoms.

7. Should a serum RF be ordered?

Rheumatoid factors (RF) are circulating immunoglobulins which recognise the Fc portion of immunoglobulin G (IgG). RF can be of a variety of isotypes, including IgG, IgM, IgA, and IgE, although, IgM is the most common form.

In patients with RA, the sensitivity of this test is in the order of 60% to 90%. This varies in terms of severity and duration of disease. At the same time, one must consider the rate of RF found in the general population is 1% to 5%. Therefore, this test is not useful in confirming or ruling out RA. It does have some value in prognostication, as well as predicting those patients at higher risk of developing some of the more serious extra-articular manifestations, including vasculitis, ocular inflammation, and nodules.

There are many other diseases associated with false positive results for serum RF (Table 4). In summary, serum RF is not a very clinically useful test and is probably overused in general medicine.

8. Treatment options

Initial Treatment

Initial presentation is usually treated with simple analgesics or anti-inflammatories, including appropriate doses of acetaminophen, acetylsalicylic acid (ASA), and coxibs. Typically, high doses of NSAIDs and coxibs are required to provide relief of symptoms, yet these do not prevent joint destruction.

Checking the BP is important, as NSAIDs/coxibs can cause new onset of hypertension in 1% to 2% of individuals and aggravate hypertension in 4% to 8% if already present.

High doses of ASA may be effective and inexpensive, but they are inconvenient and associated with significant gastrointestinal (GI) problems, tinnitus, and hearing loss. Ibuprofen in doses of up to 2400 mg/day or more may also be effective. Similarly, naproxen, 1000 mg/day to 1500 mg/day, and diclofenac, 150

Table 3
Laboratory Evaluation

Useful Tests	Optional Tests
Complete Blood Count	Anti-nuclear antibodies
Urinalysis	Extractible Nuclear Antigens
Renal profile	Rheumatoid factor
Erythrocyte sedimentation rate	Iron studies (serum iron, total iron binding capacity, % saturation)
	Hepatologic viral serology
	C-reactive protein

mg/day, are commonly used NSAIDs. In recent years, there has been increasing use of coxibs including celecoxib, 200 mg/day to 400mg/day, or rofecoxib, 12.5 mg/day to 25 mg/day, to treat inflammatory arthritis because of decreased risk of significant side effects. Meloxicam, 7.5 mg/day to 15 mg/day, is a cyclooxygenase-2 selective inhibitor that has been less well studied in regards to GI outcomes and provides a less expensive alternative. Newer coxibs that are being approved may or may not offer advantages over present coxibs.

It is a good idea to obtain a baseline serum creatinine and repeat it at two to four weeks after starting high dose anti-inflammatories. Similarly, checking the BP is important as NSAIDs/coxibs can cause new onset of hypertension in 1% to 2% of individuals and aggravate hypertension in 4% to 8% if already present.

Disease-Modifying Anti-Rheumatic Drugs

The introduction of DMARDs (disease modifying agents of rheumatic disease) depends on a number of factors. RA patients with low grade inflammation are good candidates for antimalarials or sulfasalazine. Primary-care physicians should feel comfortable introducing these agents if there is a long referral time.

Antimalarials are safe and relatively inexpensive. The slow response to treatment (three to six months) may be because it takes months to get steady-state plasma concentrations. Hydroxychloroquine (200 mg/day to 400 mg/day) or chloroquine (125 mg/day to 250 mg/day) suppress disease, although the latter is associated with more ocular toxicity. Major adverse reactions include GI upset, skin rash, visual disturbance, and retinal toxicity (extremely rare at recommended doses). Funduscopic examination, colour vision, and peripheral field testing every six to twelve months is suggested.

Sulfasalazine was first studied for RA in the ‘40s, but it is only in the last 20 years that it has enjoyed widespread use. Doses of sulfasalazine, 1 g/bid, are typically used. Clinical studies have shown it to be as effective as IM gold. Side effects are common (40% to 50%) and include skin rashes, GI complaints, hepatitis, and hematologic problems (hemolytic anemia). Monitoring should include complete blood count and liver enzymes monthly for the first three months, then intermittently.

Gold salts have been used to treat rheumatic disease for over half a century. In 1960, the Empire Rheumatism Council reported the efficacy of gold salts in RA in one of the first well-controlled, double-blinded trials in rheumatology. Gold salts are typically given in weekly intramuscular injections in doses usually less than 75 mg. Dose intervals are

Table 4
Diseases Associated with Circulating Rheumatoid Factor

- Sarcoidosis
- Chronic infections: tuberculosis, leprosy, infective endocarditis, syphilis
- Pulmonary fibrosis
- Chronic liver inflammation (infectious/autoimmune)

often extended to up to four weeks in patients who respond to therapy. Common side effects include rash, stomatitis, and injection reactions. Less common, serious side effects include proteinuria, thrombocytopenia, and pulmonary hypersensitivity.

Methotrexate is a folic acid antagonist initially developed for use in neoplastic disease. Its potential for anti-rheumatic therapy was initially seen in patients with psoriasis where it has shown improvements in joint and skin disease. Methotrexate is now considered the gold standard of DMARD therapy. It is commonly used in combination with other agents, most commonly hydroxychloroquine and sulfasalazine. Most recently, it has been shown to also work synergistically with the biological therapies. Several randomised, placebo control trials have shown its superiority over placebo in clinical symp-

Table 5
Common Drugs for RA and Monitoring

Drug	Adverse Effect	Monitoring
Antimalarials	Retinopathy	Colour and peripheral vision monitoring every 6 to 12 months
Sulfasalazine	Hematologic Hepatotoxicity Nephrotoxicity	CBC Albumin, AST. ALT Urinalysis, creatinine monthly — 3 times, then intermittently
Methotrexate	Myelosuppression Hepatotoxicity Nephrotoxicit	CBC Albumin, AST, ALT Urinalysis, creatinine monthly
Leflunomide	Diarrhea Hepatotoxicty	CBC AST, ALT monthly
Etanercept	Infection	CBC as indicated
Infliximab	Infusion reaction Infection	CBC as indicated
IM GOLD	Rash Hematologic Renal	CBC Urinalysis, creatinine

CBC: Complete blood count
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase

toms and signs of disease, as well as in radiograghic progression of erosions. Methotrexate is given orally and in weekly doses of 10 mg to 20 mg. It can be given subcutaneously to increase bioavailability, as well as to reduce some of the side effects, particularly nausea. The most common side effects include nausea, oral ulcers, elevation of transaminases, and bone marrow suppression (Table 5). Rarely, interstitial pneumonitis can develop.

"First generation" biologics have shown disease-modifying properties, as well as clinical results superior to previous therapies for RA.

Leflunomide is a recently developed ixoxazole derivative which inhibits the pyrimidine synthesis pathway in actively dividing cells. It has been shown to reduce the signs and symptoms of disease, as well as to reduce radiographic progression. Leflunomide is given orally in doses of 10 mg/day to 20mg/day. Loading doses of 100 mg daily for three days has been recommended to reach a steady state quickly, however, these doses are often associated with significant GI symptoms, particularly diarrhea. Common side effects include nausea, diarrhea, weight loss, and elevation in liver transaminases. It has not been associated with interstitial pneumonitis.

Biological Therapy

In the past few years, several novel treatments for RA have been developed. These agents use our increasing knowledge of the biological pathways, which lead to inflammatory disorders like RA.

Novel therapies have been developed to target different levels of the inflammatory cascade, including inflammatory cytokines, signal transduction peptides, cellular adhesion molecules, as well as cell lines themselves. Although many such therapies are in development, drugs targeting TNFa, and IL-1 are now available.

Etanercept is a soluble TNFa receptor antagonist which binds TNFa and is cleared from circulation. This agent is given subcutaneously twice week-

ly. Infliximab is a monoclonal antibody directed against TNFa. It is given intravenously every six to eight weeks once clinical response is reached. Kineret™ is a soluble IL-1 receptor which binds IL-1, allowing clearance from the circulation; it is given daily subcutaneously. These "first generation" biologics have shown disease modifying properties (slowing of radiographic progression), as well as clinical results superior to previous therapies for RA. They are commonly used in combination with other standard DMARDs, especially methotrexate, showing synergistic efficacy. The most common side effects relate to injection site or infusion reactions (usually self-limited). Immunosuppression resulting in infection is also a concern, although does not appear to be any more common than with methotrexate, the gold standard of pharmacologic therapy. Drug cost is also a major limitation to biologic therapy.

9. How should a patient be monitored?

Most patients with RA requiring DMARD therapy should be followed at intervals no longer than every three months, once stabilised on therapy. Focused assessment of general well-being, current joint symptoms, reponse to and/or side effects of medications, as well as inquiry regarding extra-articular disease manifestations should be made. Examination for active and damaged joint counts, as for extraarticular features, should be made at these assessments. Periodic radiographs to assess for progression of joint damage (no more than yearly) can also be useful. Drug monitoring varies according to therapy (Table 5).

10. When is a referral needed?

Aggressive therapy has been shown to affect both the short-term well-being of patients, as well as the long-term outcome especially in terms of joint damage. Delay in initiation of DMARD therapy will result in faster rates of disease progression. Several studies have also shown that therapy initiated early is not only more likely to result in clinical improvement, but is also better tolerated. Early initiation of DMARD therapy is also much more likely to result in sustained remission from disease, an ideal situation rarely seen once disease is well established. If the treating physician is unfamiliar with DMARD therapy, referral should be made early.

The differential diagnosis of the presentation of polyarthritis is broad. If doubt exists regarding a diagnosis, referral should be made. Ideally a patient presenting with RA should be initiated on DMARD therapy within three months. CME

References are available upon request—contact *The Canadian Journal of CME* at **cme@sta.ca**.