Trainee Section

Problem based review: The patient with recent onset Polyarthritis

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Abstract

A wide variety of conditions can present as acute polyarthritis, ranging from those that are potentially life threatening, to those that are self-limiting, and those that represent the early stages of a persistent and potentially destructive form of arthritis. In this article, we describe the diagnostic approach and initial management of patients with recent onset polyarthritis, with the aid of an illustrative case vignette.

Keywords

Polyarthritis, evaluation, management

Learning Points

- Septic arthritis should *not* be considered to have been excluded even if multiple joints are involved, the patient is afebrile, and the white cell count is normal, especially in patients with long-standing rheumatoid arthritis or systemic lupus erythematosus.
- Viral polyarthritis should be considered in patients with prodromal illness, "flu like" symptoms, and skin rash.
- Gout should be considered in men and elderly women with involvement of the more distal joints, and risk factors such as alcoholism and diuretic therapy.
- Among patients with undifferentiated arthritis, disease duration longer than 12 weeks, positive rheumatoid factor or anti-cyclic citrullinated peptide antibody help to predict disease persistence, and evolution to rheumatoid arthritis.
- Normal inflammatory markers, negative autoantibody results and absence of radiographic erosive changes would not exclude a diagnosis of rheumatoid arthritis.
- Patients with suspected rheumatoid arthritis (persistent inflammatory joint symptoms for longer than 6-8 weeks) should urgently be referred to the rheumatology team.

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A 42 year old previously healthy Caucasian lady, a primary school teacher by profession, presents to the acute medical unit with an eight week history of gradually worsening pain and swelling in the small joints of her hands, wrists and shoulders. Her symptoms have recently been bad enough to prevent her from performing household chores, and going to work. She says she is "at the end of her tether". She has already been referred to the rheumatologist, but her appointment is not until the following month.

How should this problem be approached?

There are four important questions to ask when faced with a patient with polyarticular joint pains:

1. What is the distribution of joint symptoms?

1. Is the problem only affecting the appendicular skeleton or also the axial structures (such as the spine, symphysis pubis, sternoclavicular, and sacroiliac joints)?
2. Within the appendicular skeleton, is the problem affecting only the large or also the small joints (e.g. joints of the hands and feet)?
3. Which joints are affected?
4. Is the distribution symmetrical or asymmetrical?

Knowing the distribution of the joint symptoms helps to narrow down the differential diagnoses:

- **Rheumatoid arthritis (RA),** for example, only affects synovial joints, and should be considered in the differential diagnosis when patients present with symptoms in the large and small synovial joints, but not when they present with low back pain, as there are no synovial joints in the lumbar spine (hence, other causes would need to be considered).
- **Seronegative spondyloarthropathy** can present with low back or gluteal pain due to inflammation of spinal enthesis (inflammation at the sites of insertion of the ligaments or tendons on bone).
- **Osteoarthritis (OA)** should be considered when weight bearing joints such as hips and knees, or those that are subject to excessive usage such as the facet joints in the cervical and lumbar spine are affected.
- **Gout** would seldom involve the girdle joints or spine because the higher temperatures in

these joints are not conducive to uric acid crystal formation.

2. Are the symptoms suggestive of an inflammatory or a mechanical problem?

Presence of joint swelling, prolonged early morning stiffness (> 30 minutes), systemic symptoms (such as weight loss, fatigue or fever), and good response to anti-inflammatory medication would suggest that the problem is inflammatory, although none of these features is specific for inflammatory arthritis.

Patients with osteoarthritis may report joint swelling and early morning stiffness, but the joint swelling is usually hard (caused by bony proliferation) with superimposed episodes of self-limiting inflammation, and the early morning stiffness generally lasts < 30 minutes. Patients with fibromyalgia may also complain of joint swelling, but this would not be accompanied by objective evidence of synovitis.

3. What is the duration of symptoms, and sequence of development of various features?

The duration of symptoms is important to record. It might be premature to consider RA in patients with symptom duration of only a few days, whereas this possibility should strongly be considered in those with inflammatory joint symptoms that have remained persistent for longer than 12 weeks.[1,2]

There are different possible ways in which joint symptoms might evolve, and the sequence of development of various features can give important leads to the underlying cause of the presentation.

- An **additive pattern** refers to involvement of new joints while previously affected joints remain symptomatic (e.g. RA), while
- A **flitting or migratory pattern** refers to development of new joint symptoms while previously affected joints are improving (e.g. rheumatic fever, bacterial endocarditis, gonococcal arthritis, systemic lupus erythematosus [SLE], sarcoidosis),
- An **intermittent pattern** refers to brief episodes of joint symptoms with asymptomatic intervals in between (e.g. gout, palindromic arthritis).

4. Are there any extra-articular features?

A thorough history is essential to uncover any extra-articular manifestations. In particular, skin and mucous membrane symptoms such as skin rashes, photosensitivity, mouth ulcers, dry eyes and mouth, red eyes (current or past), and preceding gastrointestinal or genitourinary infection may provide vital leads to the underlying diagnosis. History of psoriasis, for example, might suggest psoriatic arthritis, while a history of preceding dysentery or sexually acquired infection might suggest reactive arthritis, and that of photosensitive skin rashes, mouth ulcers, serositis and previous pregnancy loss might suggest SLE.

Box 1: Some causes of recent onset polyarthritis

- Rheumatoid arthritis
- Seronegative spondyloarthropathy (e.g. reactive arthritis, post-streptococcal arthritis, arthritis associated with inflammatory bowel disease)
- Undifferentiated arthritis
- Polyarticular septic or viral arthritis
- Polyarticular gout
- Inflammatory osteoarthritis
- Sarcoidosis
- Connective tissue diseases (e.g. systemic lupus erythematosus, Sjogren's syndrome, systemic vasculitis)
- Serum sickness
- Malignancy

Case Continued

She confirms that her hands, wrists and shoulders are painful, but denies any pain in her lower limb joints, neck and back. She says her hands have been swollen across her knuckles, and that her rings have become tighter. She feels very stiff in the mornings for the first couple of hours. She has been taking regular ibuprofen and paracetomol, but they do not seem to afford much relief. She says her symptoms began insidiously about eight weeks ago with pain in her hands, but over the next few weeks, she additionally developed pain in her shoulders. She denies any extraarticular symptoms.

She says she smokes about ten cigarettes/day, but only seldom drinks alcohol. She has never left the UK in the last three years except when she was on a 2-week holiday in Italy about six months prior to the onset of her symptoms. She has no hobbies. The relevant family history is unremarkable (including for psoriasis and inflammatory bowel disease). She lives with her husband and two children, aged 14 and 9.

What are the likely (and less likely) diagnostic possibilities at this stage?

In summary, this previously healthy middle-aged lady presents with eight weeks history of inflammatory joint symptoms, involving the small and large joints in a symmetrical fashion, and evolving in an additive pattern (note that the lack of response to ibuprofen would not exclude an inflammatory problem).

There are several possible causes of polyarthritis (see Box 1).

a) Viral infections

These should always be considered, especially in those with prodromal illness, "flu like" symptoms,

and skin rash.[3,4] The underlying viral aetiology may depend on the geographic location of the patient. Parvovirus infection is a possibility in this patient, as she might have encountered the virus at her school, and the course of the illness can indeed sometimes last several months.[5] A history of exposure to a child with a rash over the cheek ("slapped cheek" appearance) would be a particularly useful clue in favour of parvovirus infection. In patients with recent onset polyarthritis, a positive diagnosis of viral infection like parvovirus B19 may be reassuring because of its self-limiting nature. Among the other causes, hepatitis B or C, and human immunodeficiency virus seem unlikely because of her blameless past medical history, and absence of relevant risk factors. Chikungunya infection is a possibility in those who recently arrived from one of the South East Asian or African countries,[6] but this again seems unlikely in this patient because of the absence of a recent travel history (symptoms usually begin 1-12 days after the mosquito bite).

b) Polyarticular septic arthritis

It is vital not to miss this condition in patients with a shorter duration of symptoms and presence of risk factors, such as older age, diabetes mellitus and alcohol dependence, in association with fever, pain and swelling in several joints.[7] One retrospective survey that compared the presentation of polyarticular septic arthritis (n = 25) with that of monoarticular septic arthritis (n = 95) noted that the mortality was much higher among patients with polyarticular involvement (32% *v* 4%), thus highlighting the importance of not missing the diagnosis.[8] The incidence of concurrent RA, especially long-standing erosive disease treated with corticosteroids, was much higher among those with polyarticular septic arthritis (52% *v* 6%). About 20% of the patients were afebrile, and more than a third had normal white cell counts. Hence, septic arthritis should *not* be considered to have been excluded even if multiple joints are involved, the patient is afebrile, and the white cell count is normal, especially in patients with long-standing RA or SLE. Staphylococcus was the commonest cause, followed by Streptococci and Gram negative bacilli, and the skin was the usual source of infection. Polyarticular septic arthritis is unlikely in our patient because of her previous excellent health, the longer duration of symptoms, and pattern of evolution.

c) Reactive arthritis

Infectious agents can also cause a sterile reactive arthritis through immune mechanisms, in genetically predisposed individuals. Reactive arthritis presents in younger patients (peak incidence at 27-34 years), usually as asymmetrical oligoarthritis in the lower limbs, following a gastrointestinal or genitourinary infection within the preceding four weeks.[9] Additional features may include enthesitis (e.g. Achilles tendinitis or plantar fasciitis), dactylitis ('sausage' like swelling of the whole finger or toe due to extension of inflammation beyond the joint margins), spondylitis and sacroileitis (due to spinal enthesitis), and extra-articular manifestations such as recurrent uveitis. Although about 50% of patients with reactive arthritis do not recall the preceding infection, the predominant involvement of the upper limb joints in this patient is not typical of reactive arthritis.

Post-streptococcal reactive arthritis (PSRA) is an entity distinct from acute rheumatic fever and other forms of reactive arthritis.[10] It can present with polyarthritis, following Group A streptococcal throat infection. Reactive arthritis due to tuberculosis has also been described ***(Poncet's disease)***,[11] but is rare in the UK. ***Inflammatory bowel disease related arthritis*** can also present with acute polyarthritis,[12] but this too would seem unlikely because of the absence of overt gastrointestinal manifestations.

d) Gout

This can present with polyarticular involvement, but this would be extremely unlikely in this patient because [a] she is premenopausal, [b] involvement of the shoulder is rare (see above), and [c] symptoms would not persist for this long.[13] Gout would, however, need to be considered in men and elderly women with shorter duration of symptoms, involvement of the more distal joints, and appropriate risk factors (e.g. alcoholism, diuretic therapy, cardiovascular risk factors). Although subsequent rather than initial attacks tend to be polyarticular, the absence of a previous history of gout would not exclude this diagnosis.[14,15] Just as with monoarticular involvement, the diagnosis of polyarticular gout would not exclude septic arthritis, as both could co-exist.[16]

e) Inflammatory osteoarthritis is another differential,[17] but the presentation with gradual worsening of symptoms over eight weeks, especially in an additive pattern, and involvement of the wrists, are not typical.

The absence of extra-articular symptoms makes it unlikely that her symptoms are due to a form of ***systemic disease*** such as sarcoidosis, SLE, Sjogren's syndrome, scleroderma, or systemic vasculitis. She hasn't been exposed to any ***drugs*** that are known to cause inflammatory arthritis (e.g. minocycline)[18] nor does she have any hobbies that would expose her to unusual infections (e.g. Lyme disease).[19] Apart from parvovirus B19 and possibly, PSRA, we are therefore

now left with only ***undifferentiated arthritis***, and the key practical question to ask is whether this inflammation would remit spontaneously, or remain persistent and lead to joint damage in the long-term (or in other words, evolve into RA).

Several studies have demonstrated that among patients with undifferentiated arthritis, positive autoantibodies (see later) and/or the presence of radiographic erosions help to predict persistence and development of RA.[20-22] In those with negative test results for antibodies and absence of erosions, duration of inflammatory joint symptoms > 12 weeks helps to predict disease persistence.[23] Early diagnosis of RA is important because [a] irreversible joint damage occurs early, [b] early treatment with disease modifying drug therapy improves both short and long-term clinical, radiological and functional outcomes, and [c] a delay of even a few months in commencing disease modifying therapy can have a significant adverse impact on long-term outcome.[24-27]

What should be done next?

The patient should be examined to confirm the presence of synovitis, and determine its extent and distribution. Some early signs of RA in the hands include

- Spindled appearance of the proximal interphalangeal (PIP) joints. Because the synovial inflammation in RA is "intracapsular", any fluid collection or soft tissue swelling would distend the capsule to result in a spindled appearance.
- Loss of the valleys between the heads of the metacarpal bones (this would be easier to detect if the patient is asked to make a fist).
- Tenderness on squeezing the metacarpophalangeal (MCP) joints.
- Swelling around the ulnar styloid process.
- Extensor tenosynovitis (visible as a linear swelling along the dorsum of the wrist).
- Carpal tunnel syndrome (caused by swelling of the flexor tendon sheath within the carpal tunnel).

Physical signs of synovitis may be difficult to appreciate in obese patients, those in whom the symptoms are intermittent, and in those who have recently received corticosteroids.[2] In the feet, the only sign may be tenderness on squeezing the metatarsophalangeal (MTP) joint.

A thorough examination is essential to uncover any extra-articular manifestations such as psoriasis in the skin or nails, vasculitic skin rashes, subcutaneous nodules (although rarely present in the early phase of the disease), erythema nodosum, or evidence of interstitial lung disease.

Case Continued

On examination, there is evidence of synovitis in a few of her PIP and MCP joints, and also around the right ulnar styloid process. MCP joints are bilaterally tender on squeezing. There is restricted movement of both wrists and shoulders. The rest of the examination is normal.

What tests should be requested?

Full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver and renal panel, urinalysis, rheumatoid factor (RF), cyclic citrullinated peptide antibody (anti-CCP), and anti-nuclear antibody (ANA) should be requested.[28]

Among patients with recent onset polyarthritis, routine serological testing for viral infection does not contribute significantly to the diagnosis.[29,30] This patient should probably be tested for parvovirus B19, but testing for hepatitis B or HIV is not necessary because of the absence of relevant risk factors. Anti-Streptolysin-O (ASO) titre may be helpful to diagnose PSRA.

Although not an essential investigation in the acute setting, plain x-rays of the hands and feet could be requested to look for erosive changes (or at least to serve as a baseline for future comparison).[28] Plain x-rays of the feet would be useful even in the absence of symptoms in the feet, as erosions occur earlier in the feet.[31] Plain radiographs taken during the early phase of RA may, however, only show soft tissue swelling and periarticular osteoporosis. Plain x-rays of the larger joints such as shoulders add little diagnostic information, and need not be requested routinely. A chest x-ray should also be requested as a routine (as a baseline because of the small risk of pneumonitis with methotrexate, and also to look for any evidence of occult tuberculosis).

Case Continued

The following results are obtained:
Haemoglobin 11.8 gm/dl (mean corpuscular volume 84)
White cell count 7.2 x 10^9/L
Platelet count 534 x 10^9/L
ESR 76 mm after 1 hour
CRP 58 mg/L
Liver and renal panel normal
Urinalysis normal
RF negative
ANA negative
Anti-CCP is strongly positive
Parvovirus B19 IgM negative
ASO titre normal

Plain x-rays of the hands and feet show soft tissue swelling around several PIP and MCP joints and evidence of periarticular osteopenia, but there are no erosive changes.

Chest x-ray shows normal heart shadow and clear lung fields.

How could these results be interpreted?

Normocytic anaemia, thrombocytosis, and the elevated ESR and CRP support the clinical impression of an inflammatory problem. It should be noted that inflammatory markers such as ESR or CRP can be normal in more than half of the patients with RA during the early phase.[32]

Negative RF would not exclude RA, as it may be absent in about a third of patients with RA, and in more than half of them during the first six months from disease onset.[2] Negative ANA would however make SLE extremely unlikely because of its excellent sensitivity (> 99%).[33] The normal parvovirus serology and ASO titre would exclude parvovirus B19 and PSRA respectively.

Anti-CCP is highly specific for diagnosis of RA (>96%),[34] and strongly supports the diagnosis of RA in this patient. Unlike RF, it is not present in healthy individuals, or in patients with infections or other connective tissue diseases. It predicts persistence among patients with early undifferentiated arthritis, and increases the likelihood of erosive damage [35]. Sensitivity is, however, low (~ 60%). Hence, even if the anti-CCP result had been negative in this patient, it would not have helped to exclude RA.

The radiographic changes support the impression of inflammatory arthritis. The absence of erosive changes would not exclude RA because it takes time for plain radiographic erosive changes to manifest.[36] The rheumatologist might decide to perform an ultrasound examination of the joints, as it can detect early inflammatory changes such as synovitis and increased synovial blood flow [Doppler ultrasound]. Ultrasound has also been shown to be more sensitive than plain x-rays in detecting erosions.

How should this patient be managed in the acute setting?

She should be urgently referred to the rheumatologist so that she could be commenced on disease modifying drug therapy after appropriate assessment. Patients with joint pains that have persisted for longer than 6-8 weeks should be referred to the rheumatologist when any of the following features are present:[1,2]

- Joint swelling
- Early morning stiffness lasting > 30 minutes
- Involvement of the MCP and MTP joints (as evidenced by pain on compression of these joints)
- Elevated inflammatory markers
- Positive rheumatoid factor or CCP antibody.

Normal inflammatory markers, negative serology and normal plain radiographs should not delay referral in the presence of inflammatory joint symptoms.

Because this patient is already on paracetamol, addition of codeine or tramadol might help to control the pain, but the use of stronger analgesics such as morphine should be discouraged. Tramadol possesses several advantages over codeine, such as less addictive potential, and reduced risk of drowsiness, constipation, and respiratory depression. In addition, the serotonin-norepinephrine reuptake inhibiting property of tramadol may help those with associated fibromyalgia.

A non-steroidal anti-inflammatory drug is more effective than simple analgesics, but the benefits should be balanced against their potential to cause gastrointestinal, renal and cardiovascular risk.[37,38] They may not be the ideal choice in the presence of risk factors such as old age (> 65 years), peptic ulcer disease, renal impairment, concomitant anti-coagulant therapy, congestive heart failure, hypertension, asthma, pregnancy or breast feeding. The recommendation is to use the lowest possible for the shortest possible duration. Because of concerns about the increased thrombotic risk, especially with the use of selective cyclooxygenase-2 inhibitors, they should be avoided in patients with known ischemic heart disease or stroke, and used with caution in those with cardiovascular risk factors.[39] In patients with risk factors for peptic ulcer, a proton pump inhibitor should be co-prescribed.[40]

Systemic corticosteroids are useful as 'bridging therapy' (during the lag time that it takes for a disease modifying drug to take effect) to control disease activity among patients with active disease in multiple joints and limitation of function.[37,41] However, if the diagnosis is uncertain, or if the patient is shortly due to be assessed by a rheumatologist, it is never a good idea to administer corticosteroids. Whenever possible, a rheumatologist should be consulted (at least via phone) before giving corticosteroids. If the decision is taken to commence corticosteroids, one option would be to administer 80-120 mg of methylprednisolone intramuscularly (the effect may last about 3-4 weeks). Alternatively, oral prednisolone could be commenced in a dose of < 10-15 mg/ day (the practice of giving 40 mg/day for 5 days should be discouraged, as such a high dose is not necessary for controlling joint inflammation, and also, the abrupt discontinuation might lead to a rebound of joint symptoms).

What other measures are helpful in patients with early rheumatoid arthritis?

Many patients with RA complain of poor sleep, excessive daytime tiredness, and widespread body pain that is out of proportion to any joint inflammation ("fibromyalgia"), and symptoms of depression. These symptoms would need to be addressed with appropriate therapy including

tricyclic anti-depressant therapy (e.g. low dose amitriptyline), selective serotonin reuptake inhibitors (e.g. fluoxetine), graded exercise program, and cognitive behavioural therapy.[42]

Input of the physiotherapist and occupational therapist is helpful for patients with RA.[42] Occupational therapists can provide advice on joint protection, splints, assistive devices, and modification of home or work environment, while physiotherapists can teach exercises to improve or maintain range of movements in the joints. Input of the orthotist (or podiatrist) is also helpful for patients with metatarsal pain so that they can be provided with appropriate foot wear and insoles.

Accelerated atherosclerosis is more prevalent among patients with RA, and is promoted by uncontrolled systemic inflammation.[43] Mortality is increased among patients with RA, mainly because of ischemic heart disease. Traditional risk factors such as smoking, obesity, hypertension, diabetes mellitus, and hyperlipidemia should therefore be addressed, in addition to controlling disease activity.[44]

Case Outcome

She is given 120 mg of methylprednisolone intramuscularly, following which she experiences good symptom relief. She is subsequently seen by the rheumatologist, who commences her on methotrexate after appropriate counselling. She is told that methotrexate could be associated with gastrointestinal side effects such as mouth ulcers and nausea, bone marrow and liver toxicity, teratogenicity, and hypersensitivity pneumonitis. Because she is sexually active, she is advised to follow a reliable method of contraception. She is also advised to have regular blood tests to detect liver and bone marrow toxicity early, and to take folic acid once weekly to reduce gastrointestinal, liver and bone marrow toxicity.

She is referred to the occupational therapist so that her difficulties with hand function could be addressed. She is advised to quit smoking. Her body mass index is 24, with blood pressure of 124/76 mm Hg, and satisfactory fasting blood glucose and lipid profile.

Three months after commencing methotrexate, her disease activity is low, and she is able to wean herself off the ibuprofen. She is able to tolerate 20 mg/week of methotrexate well, and her blood monitoring remains satisfactory. Her ESR is reduced to 16, and CRP to less than 5. However, she has been unable to quit smoking, and hence, is referred to the smoking cessation service.

Conflicts of interest

None of the authors have any conflicts of interest to declare.

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