Diagnosis of early rheumatoid arthritis: what the non-specialist needs to know

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects about 1% of the population. It leads to irreversible joint damage and systemic complications, and the age-adjusted mortality of those affected exceeds that of the general population.^{1–3} When joint damage was seen to be an early feature of the disease,^{4–12} rheumatologists put forward the point at which they prescribed disease-modifying antirheumatic drugs (DMARD), in the hope of slowing or even arresting disease progression. Patients in whom DMARD therapy is introduced early have better function and radiological outcome in the long-term than those in whom it is delayed.^{13–19} It was for these reasons that a SIGN (Scottish Intercollegiate Guideline Network) guideline²⁰ in 2000 indicated that a patient with inflammatory arthritis lasting >6–8 weeks should be referred for a specialist (rheumatology) opinion. However, a recent audit in our unit showed that such patients were referred after a mean of 16 weeks (interquartile range 6–34) from onset of symptoms.²¹ Other studies suggest that the long lag between symptom onset and the diagnosis of RA is mainly due to late referral rather than patient delay in reporting symptoms or long waits for outpatient appointments.²² Moreover, in most referral letters from general practitioners, a tentative rheumatological diagnosis is either not stated or stated wrongly.^{23,24} The reason is clear: RA has no disease-specific diagnostic features²⁵ and patients can present with a wide range of manifestations. In this article I discuss the difficulties of early diagnosis, taking an illustrative case of polyarthritis (inflammation of more than four joints), the commonest presentation.

ONSET

The onset of polyarthritis in RA is insidious in about three-quarters of patients and initially affects the small joints of the hands and feet (metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints) before spreading to the larger joints. The following are atypical manifestations.

- *Polymyalgic onset*—The patient is usually elderly and presents acutely with stiffness predominantly around the shoulders and pelvic girdle. The erythrocyte sedimentation rate (ESR) is usually raised. There is a good response to low-dose corticosteroids (prednisolone 15–20 mg a day)
- *Palindromic onset*—The patient experiences recurrent episodes of pain, swelling and redness affecting any one joint or several joints at a time, each lasting only a day or two. Symptoms may later become persistent
- *Systemic onset*—The first complaint is non-focal, such as weight loss, fatigue, depression, or fever, or relates to an extra-articular feature such as serositis or vasculitis. Articular manifestations may be absent to start with
- *Persistent monoarthritis*—The patient initially has persistent arthritis affecting a single large joint such as knee, shoulder, ankle or wrist.

ILLUSTRATIVE CASE OF POLYARTHRITIS

A woman schoolteacher, aged 30, has for twelve weeks been troubled by pain and swelling in the small joints of her hands and feet. She says that her hands are stiff in the early mornings for a couple of hours and then improve gradually in the course of the day. Her sleep is sometimes disturbed by pain, and she feels very tired during the day. Previously she was fit and well: there is no personal or family history of psoriasis or inflammatory bowel disease and she was not knowingly exposed to infections before the onset of this illness. She lives with her husband and two children, aged 6 and 4, and her symptoms interfere with some activities of daily living. On examination her metacarpophalangeal joints (MCP) are swollen and tender bilaterally, as are a few of the proximal interphalangeal joints (PIP) in both hands. Compression of metatarsophalangeal joints (MTP) causes pain. All her other joints are clinically normal and the examination reveals nothing else of note. Blood investigations, including liver function tests, give normal results apart from an ESR of 28 mm/h. Antibodies to parvovirus are not found, and rheumatoid factor and antinuclear antibody are likewise absent. On plain radiographs of the hands and feet the only abnormality is periarticular soft tissue swelling around a few PIP joints.

Box 1 Features suggestive of inflammatory arthritis

- History of joint swelling, early morning stiffness lasting ≥ 30 minutes, systemic symptoms such as tiredness, malaise, low-grade fever or weight loss, improvement of symptoms with anti-inflammatory medication
- Objective evidence of joint swelling and tenderness on examination
- Raised ESR or CRP, normocytic normochromic anaemia, thrombocytosis, low albumin, raised alkaline phosphatase

DIFFICULTIES IN DIAGNOSIS OF RHEUMATOID ARTHRITIS**Clinical diagnosis of inflammatory arthritis is not always straightforward**

The history of swelling in joints, early morning stiffness lasting > 30 minutes, systemic symptoms such as tiredness combined with objective evidence of synovitis would favour a diagnosis of inflammatory arthritis (Box 1). However, reality can be more complex:

- Objective signs may be lacking or have been suppressed by anti-inflammatory medication
- Joint swelling can be difficult to identify in obese patients
- The sensation that joints are swollen may be reported even by some patients with fibromyalgia
- Osteoarthritis as well as RA can cause morning stiffness, though in osteoarthritis it usually lasts less than 30 minutes
- Inflammatory markers such as the ESR or C-reactive protein (CRP) are normal in about 60% of patients with early RA²⁶
- In a patient with preceding osteoarthritis, radiographic changes can be misleading, especially if those suggestive of inflammatory arthritis have not yet developed.

The classic features of rheumatoid arthritis take time to develop

The most important question, in our patient, is whether she has a potentially damaging disease such as RA. The answer is not always obvious since RA in its early stages tends not to fit the textbook description. For example, seropositivity for rheumatoid factor, radiographic erosions and subcutaneous nodules are all absent. As mentioned above, at the time of presentation many patients with RA have normal inflammatory markers; moreover, about 60% are seronegative for rheumatoid factor and more than 70% have normal plain radiographs.²⁶ Thus negative results with these do not exclude the diagnosis. In our patient, reasons for strongly suspecting RA are the longstanding inflammatory symptoms (twelve weeks) and the symmetrical involvement

of MCP, PIP and MTP joints—joints that are commonly affected in RA.

A wide variety of conditions can present as inflammatory arthritis

The other difficulty is the wide differential diagnosis of polyarthritis (Box 2). A good history and physical examination combined with a few simple laboratory or radiological investigations should help in excluding most of the conditions that mimic RA. In our patients, the following need to be considered:

- *Postviral arthritis*—Parvovirus arthritis should be considered, since she may have encountered the virus at her school. However, against this diagnosis are the duration of joint symptoms (which with parvovirus seldom last more than eight weeks), the fact that she did not have fever, rash or sore throat and the negative parvovirus serology
- *Seronegative spondyloarthritis*—In this condition one would expect features such as psoriasis, inflammatory bowel disease or inflammatory back pain and a family history of similar disorders. However, a small proportion of patients with psoriatic arthritis do get arthritis before skin lesions appear.

Box 2 Conditions that can present as polyarthritis and mimic RA

Postviral arthritis—e.g. parvovirus, mumps, rubella, hepatitis B and C
 Seronegative spondyloarthritis—e.g. psoriatic arthritis, inflammatory bowel disease
 Connective tissue diseases—e.g. systemic lupus erythematosus, scleroderma, vasculitis
 Osteoarthritis
 Crystal arthritis—e.g. polyarticular gout, pseudogout
 Miscellaneous—e.g. sarcoidosis, thyroid disease, infective endocarditis, malignant disease

Box 3 Investigations that may help in diagnosing common underlying causes of polyarthritis

- Rheumatoid factor—positive in only 70% of patients with RA and present in various other inflammatory diseases and sometimes in health
- Antinuclear antibody—good screening test for SLE but sometimes positive in conditions including RA and in health
- Urinalysis—microscopic haematuria/proteinuria can indicate connective tissue disease
- Viral antibody titres—parvovirus, hepatitis
- Serum urate/synovial fluid analysis—to exclude gout
- Plain radiographs of hands and feet—can be normal in early RA or show periarticular soft tissue swelling/osteopenia/marginal erosions; erosions occur earlier in feet, so the feet should be X-rayed even in patients without foot symptoms

- *Systemic lupus erythematosus*—This diagnosis is made unlikely by the absence of extra-articular features such as facial butterfly rash, photosensitivity, hair loss, mouth ulcers, dry eyes and mouth, Raynaud's phenomenon, pleurisy or pericarditis, nephritis, thrombocytopenia or myositis together with the negative antinuclear antibody test.

The other conditions listed in Box 2 are much less likely in view of the patient's age and sex and the absence of other systemic manifestations. Since her clinical picture is not consistent with any of the specific entities she cannot yet be diagnosed as having RA; at this stage the label of 'early polyarthritis' is more appropriate.

Not all patients with 'early polyarthritis' develop persistent disease

When a patient with inflammatory arthritis cannot definitely be labelled as having RA, it becomes important to decide whether the arthritis is likely to remit or to persist. Clearly, if spontaneous remission seems likely, the patient should be spared potentially toxic DMARD therapy. On the other hand, a patient with persistent inflammation should be started promptly on DMARDs since the condition may represent RA in evolution. From the Norfolk Arthritis Register²⁷ there is evidence that an overwhelming majority of patients with persistent polyarthritis in due course come to satisfy diagnostic criteria for RA²⁸ (from 47% at baseline to 93% after 5 years).¹³ Thus, since joint damage and functional loss occur early,^{3–12} most patients develop these irreversible changes before a definite diagnosis of RA can be made.

How can the clinician predict persistence of disease? Several research groups have tried to identify pointers in patients with early arthritis^{29–34} but their results are not easily combined because of heterogeneity in populations, predictive factors used and duration of follow-up. Among the predictive factors suggested, the most useful seems to be disease duration exceeding 12 weeks: a patient who has had inflammatory joint symptoms for this long is very unlikely to experience a spontaneous remission. Other features suggesting the unlikelihood of remission are positive tests for rheumatoid factor or cyclic citrullinated peptide antibodies and the presence of erosions on radiographs.

WHICH PATIENTS SHOULD BE REFERRED?

Early treatment of RA can be a realistic goal only if general practitioners and other non-rheumatologists recognize the clinical picture of early inflammatory arthritis and refer patients promptly for a specialist opinion. Patients with joint pains that have persisted for more than 6–8 weeks

should be referred especially in the presence of the following features:

- Joint swelling
- Early morning stiffness ≥ 30 minutes³⁵
- Involvement of metacarpophalangeal and metatarsophalangeal joints (evidenced by pain on compression of these joints)³⁵
- Systemic symptoms such as fatigue or weight loss
- Raised inflammatory markers
- Positive rheumatoid factor.

Normal inflammatory markers, negative serology and normal plain radiographs are not valid reasons for delaying referral since RA is diagnosed on the basis of symptoms and signs.

Should general practitioners start DMARDs themselves? According to one survey many are reluctant, preferring to get a specialist opinion first.³⁶ The results of our audit²¹ have reinforced this impression: only 10% of eligible patients had a DMARD prescribed by the general practitioner before their first clinic appointment; moreover, there is evidence that patients managed by rheumatologists do better than those strictly managed by non-rheumatologists.³⁷ Thus, in a patient with suspected RA or 'RA-like' polyarthritis, the message of this paper is: refer early to a rheumatologist.

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