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POLYARTHRITIS: IS IT RHEUMATOID DISEASE?*

N. P. Hurst,† Western General Hospital, Edinburgh

The differential diagnosis in a patient with a short history of polyarthritis contains a number of pitfalls for the unwary physician. The recognition of a typical pattern or cluster of clinical features is an essential skill in diagnosing rheumatic disease; these include the mode of onset, the anatomical distribution of joint involvement (Table 1), the presence or absence of extra-articular features such as rashes or ocular inflammation (Table 2) and, in some instances such as ankylosing spondylitis and psoriasis, a family history of the disease. With a short history of polyarthritis there may be very few clues and a precise diagnosis may be difficult to achieve.

How may rheumatoid arthritis (RA) be distinguished in it's natural history from other common arthropathies, so that prompt and effective disease modifying therapy can be initiated? Unfortunately there is no specific diagnostic laboratory test for RA; diagnosis is based on clinical features, supported where possible by laboratory evidence. In diagnosing RA at an early stage the rheumatologist often has to apply more clinical art than science to distinguish it from other forms of arthritis.

TABLE 1

Typical anatomical patterns of synovitis in chronic inflammatory joint disease

POLYARTICULAR	
MCP, PIP and MTP joints ± larger joints	RA, SLE, psoriasis
DIP joints	psoriasis
OLIGOARTICULAR (asymmetrical)	
Large joints more frequently than small joints	psoriasis, spondylarthritis
MONOARTICULAR	
Small or large joint	psoriasis, spondylarthritis, chronic infection

MCP, metacarpophalangeal; PIP, proximal interphalangeal; MTP, metatarsophalangeal; DIP, distal interphalangeal; SLE, systemic lupus erythematosis.

TABLE 2

Extra-articular features associated with inflammatory joint disease

Rheumatoid arthritis	Subcutaneous nodules, sicca syndrome, pleural effusion, Raynaud's phenomenon (usually mild)
Septic lupus erythematosis	Raynaud's phenomenon, serositis, alopecia, photosensitive rashes, fever
Reactive arthritis	Urethritis, conjunctivitis, fever, psoriasiform rash, diarrhoea, iritis
Ankylosing spondylitis	Iritis
Sarcoidosis	Erythema nodosum

*Based upon a lecture delivered at the Symposium on *Rheumatoid Arthritis* held in the College on 28 September 1994.

†Consultant Rheumatologist.

POINTERS IN FAVOUR OF RHEUMATOID ARTHRITIS

The 1987 revised criteria for classification of RA[1] (Table 3) are invaluable in epidemiology and research, but in clinical practice a provisional working diagnosis of RA is often made without strict fulfilment of these criteria.

Clinical features

Clinical pointers which favour a diagnosis of RA include symptoms of joint inflammation such as early morning stiffness of joints, symmetrical tenderness and synovial swelling of one or more of the following groups of joints—MCP, PIP, wrists, or MTP; other larger peripheral joints may or may not be involved initially. Within each of these groups, not all joints may be involved. If there is marked asymmetry of involvement, such as one or two MCP joints on one hand and one PIP in the other hand, or atypical joints such as distal IP's or a single large joint are affected, other diagnoses such as psoriatic arthritis or spondylarthritis should be considered. The difficulties encountered in diagnosing patients with atypical patterns of joint involvement are discussed later.

In general, extra-articular features are not a feature of early RA and are more likely to be found in well established seropositive disease. For example, mild Raynaud's phenomenon, while not uncommon in established RA, is usually absent at presentation. Indeed, if marked Raynaud's phenomenon is present this increases the likelihood of alternative diagnoses[2] such as systemic lupus erythematosus (SLE),[3] mixed connective tissue disease (MCTD),[4] or more rare conditions such as progressive systemic sclerosis (PSS).[5] Subcutaneous nodules are an important diagnostic feature, and they are almost invariably associated with a positive rheumatoid factor test.[6] However, they are not often found in patients with a very short history of RA,[7] and only rarely precede the onset of synovitis or occur in it's absence.[8] Pleural effusion is uncommon but, when present, is found especially in males with early seropositive RA.[9,10] In either sex, polyarthritis associated with pleural effusion or serositis has a wide differential diagnosis which includes neoplasia, chronic infection such as tuberculosis or connective tissue diseases such as SLE. Evidence of skin disease, particularly psoriasis or photosensitive rashes, may provide an important clue to diagnosis. Less specific clinical findings such as fever or weight loss, although certainly compatible with a diagnosis of RA and particularly those with more active and aggressive disease, should also alert one to consider alternative diagnoses such as SLE or related connective tissue diseases, systemic vasculitis, and arthropathies associated with chronic infection or malignancy.

TABLE 3

1987 revised criteria for the classification of rheumatoid arthritis[1]

A patient may be classified as having RA if 4 of the following 7 criteria are present, with criteria 1 to 4 being present for at least 6 weeks:

1. Morning stiffness ≥ 1 hour
2. Soft tissue swelling (arthritis) of 3 or more joint areas
3. Swelling (arthritis) of PIP, MCP joints or wrists
4. Symmetric swelling (arthritis)
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic erosions and/or periarticular osteopenia in hands/wrists

Family history
This may be helpful in diagnosis, as immunogenetic factors play a significant role in susceptibility to rheumatic disease including RA[11,12] The knowledge that one or more of the first degree relatives of a patient with early synovitis have RA increases the probability that the patient may have RA. However as RA is a common disorder, it's presence in the family may be fortuitous and have no bearing on the patient's diagnosis. Indeed it may be the patient's anxiety about their family history which has led them to report trivial musculoskeletal symptoms to their doctor.

Laboratory tests
The most important diagnostic investigations where early RA is suspected are tests for rheumatoid factor (RF), antinuclear factor (ANF) and radiographs of the hands, wrists and feet. There are a number of methods for detecting RF.[13,14] The widely used RA latex test is sensitive but not very specific for RA. Not infrequently this test is weakly positive in normal individuals, and may be strongly positive in a number of chronic inflammatory disorders associated with joint symptoms (Table 4). The Rose–Waaler test is less sensitive than the latex test and much more specific for RA, but even this may occasionally give false positive results in conditions such as SLE or systemic vasculitis. Conversely, a negative RF test does not exclude RA and 20 to 25 per cent of patients remain seronegative throughout their clinical course.[14] Whichever of the various tests for RF is used, the result can only be interpreted in the light of the clinical picture. The importance of the ANF test is to help to distinguish those patients who have SLE rather than RA, but it should be remembered that about 30 per cent of patients with seropositive RA also have a positive ANF.[14]

TABLE 4

Conditions other than rheumatoid arthritis with arthralgia and positive tests for rheumatoid factor

Systemic lupus erythematosus
Mixed connective tissue disease
Sjogren's syndrome
Sarcoidosis
Fibrosing alveolitis
Systemic vasculitis
Chronic infection
(e.g. bacterial endocarditis, syphilis, leprosy)
Viral infection
(e.g. EB-virus, HIV, Hep BV, Hep CV)

Radiography
Examination of hands, wrists and feet may be very helpful in the diagnosis of early RA. Radiographic changes include soft tissue swelling, periarticular osteoporosis, loss of articular cartilage and erosions in periarticular bone. The latter usually take time to develop but may occasionally appear rapidly and be apparent even in early RA. When radiographs are normal, or there are only non-specific changes such as periarticular osteoporosis, the films are useful in providing a baseline for future comparison. Sometimes the films show old established erosive changes even though the history is apparently short. For example the patient may have had an earlier and long forgotten episode of metatarsalgia due to transient MTPJ synovitis; such episodes often leave behind radiological evidence of rheumatoid erosions that help to confirm the diagnosis. Unfortunately even apparently 'typical' erosions are not completely diagnostic! Similar radiographic evidence of bone erosion in small peripheral joints may sometimes be associated with psoriatic arthritis,[15] reactive arthritis[16] or ankylosing spondylitis,[17] once again emphasising the over-riding importance of interpreting investigations in the clinical context.

CONDITIONS SOMETIMES CONFUSED WITH RA AT PRESENTATION

There are a number of rheumatic disorders which may be confused with RA at the time of presentation (Table 5). In theory these conditions should be easy to distinguish but in practice cause difficulty either because they have features resembling RA or because important distinguishing features are overlooked. For example, some patients with benign joint hypermobility syndrome present with arthralgia and stiffness which is easily confused with polyarthritis unless the signs of hypermobility[18] are recognised. Some of the clinical features of other conditions which may be confused with RA are described as follows but it is not intended to comprehensively review each condition.

TABLE 5

Conditions sometimes confused with rheumatoid arthritis at presentation

Younger patients
viral arthritis
psoriatic
SLE, other corrective tissue diseases
spondylarthritis
benign hypermobility syndrome
psychogenic rheumatism (somatisation disorder)
Very uncommon
systemic vasculitis
Middle-aged or older patients
early generalised nodal osteoarthritis
'pseudo-RA' pattern of osteoarthritis

Viral arthritis
This is often included at the top of the physician's differential diagnosis of early polyarthritis, but in practice, although many viruses can cause polyarthritis (Table 6), true viral arthritis is probably uncommon. Polyarthritis of any cause, including RA, may be associated with nonspecific symptoms resembling viral infection which occur prior to, or coincidental with the development of joint symptoms. These symptoms, which may include malaise, myalgia and perhaps low grade fever are caused by the production of cytokines, and are entirely nonspecific. In the UK, viruses of clinical importance to rheumatologists (Table 6) include parvovirus[19,20] and rubella[21,22] which are true arthrotropic viruses, and hepatitis B and C viruses which cause polyarthritis through immune complex mediated mechanisms.

The principle clues to the presence of a viral arthritis are usually the clinical context, history of exposure and, in some patients, the presence of a typical rash

TABLE 6
Viral arthritis

Arthrotropic viruses	*Immune complex mediated arthritis*
parvovirus	hepatitis B
rubella	hepatitis C
Viruses which rarely cause arthritis	
influenza	
coxsackie	

or other specific feature. For example parvovirus usually occurs in small epidemics amongst infant school children and produces fever and a rash which quickly becomes confluent producing the so-called 'slapped cheek' appearance. The virus may cause arthritis in non-immune adults, especially females. The typical patient is often someone in frequent contact with young children, such as a primary school teacher or young mother, and other features such as rash may be absent. Rubella arthritis typically occurs in adolescents or young adults either after exposure to wild virus[21] or after immunisation;[22] as with parvovirus, the history of contact followed by the rubelliform rash and fever followed by polyarthritis are the most important clues. The diagnosis of viral arthritis should be confirmed with early and late serological tests for specific neutralising antibodies. It is often assumed that viral arthritis is short-lived but both these viruses may produce prolonged arthralgia and synovitis lasting many months; another confusing feature is that the intensity of the arthralgia may be out of proportion to the objective signs of synovitis. To avoid inducing anxiety and to facilitate rehabilitation it is important to be able to give these patients a confident diagnosis and prognosis, and appropriate supportive management.

The clinical and laboratory features of hepatitis B virus (HBV) infection have been well reviewed.[23] There is also increasing evidence that hepatitis C virus infection is implicated as a cause of mixed cryoglobulinaemia which is characterised by arthralgia, purpura and neuropathy.[24] As with HBV infection, the clinical picture should make distinction from RA very easy.

Other connective tissue diseases

SLE, MCTD and PSS may present with small joint polyarthritis resembling RA. Polyarthritis is one of the commonest presenting features of SLE or MCTD; the patient is usually female and a careful history and examination will often reveal other extra-articular clues such as serositis, rashes or Raynaud's phenomenon. Where there are no extra-articular features the main clue to the diagnosis of SLE or MCTD is likely to come from serological tests, i.e. a positive ANF test coupled with a negative rheumatoid factor test.

Psoriasis

In contrast to viral arthritis or the connective tissue diseases, psoriatic arthritis is common and is often confused with RA, mainly through failure to recognise the typical psoriatic patterns of joint involvement or failure to find the skin lesion (Table 7). One of the patterns of psoriatic arthritis is clinically identical to RA except that the patient has psoriasis and is seronegative for RF and whether this form of psoriatic arthritis is truly distinct from RA is a matter of debate. There

TABLE 7
Psoriatic arthritis

Problems in diagnosis
Failure to recognise the 'psoriatic distribution' of joint involvement
Failure to spot the skin lesion
Failure to take a family history
Some patterns of joint involvement found in psoriatic arthritis
Polyarthritis—symmetrical 'rheumatoid pattern'—but RF negative
DIPJ arthritis usually associated with nail dystrophy
Asymmetrical arthritis of small and/or large joints
Dactylitis (sausage finger or toe)
Mono- or oligoarthritis
(large joints more frequent than small joint)
Axial arthritis—e.g. SI joints, hips, spine, sternoclavicular joints

are several other patterns of joint involvement which suggest psoriatic rather than rheumatoid arthritis, and each of these patterns may occur separately or together. The commonest is probably a chronic monoarthritis or asymmetrical oligoarthritis, more frequently affecting joints in the lower limb than the upper limb. Small joints may be involved, but again usually in an asymmetrical manner. 'Sausage finger' or dactylitis of fingers or toes is another characteristic finding and is due to synovitis of both the interphalangeal joints and tendon sheaths. Dactylitis also sometimes occurs in reactive arthritis and other spondylarthritides. Inflammation of a DIP joint is characteristic of psoriatic arthritis and almost invariably occurs in the presence of psoriatic nail dystrophy—there should be no difficulty distinguishing this from RA in which DIP joint inflammation is not a prominent feature. A few patients present with an acute psoriatic monoarthritis resembling gout, but this should again be readily distinguishable from RA.

Psoriatic skin lesions may or may not be prominent in psoriatic arthritis, and may even be absent when the patient first presents. In anyone with a 'psoriatic' pattern of joint involvement, a careful search for skin lesions should include examination of the scalp, umbilicus and natal cleft. Sometimes the lesion is inconspicuous and the patient may not be aware of it's presence. When the patient appears not to have skin or nail lesions, a strong family history of psoriasis may enable a presumptive diagnosis of psoriatic arthritis. In a proportion of such patients the skin lesion may appear long after the joints have become involved.

Perhaps surprisingly, ankylosing spondylitis (AS) may be confused with RA at first presentation, particularly when there is synovitis of the small joints of hands and feet and the patient does not volunteer a history of back symptoms. As with psoriatic arthritis the relative asymmetry and patchy pattern of joint involvement should lead to consideration of AS or related conditions. Such patients may or may not complain of low back stiffness; often their back symptoms have been present for some while and the patient has come to accept them. Thus where spondylarthritis is suspected, enquiry about symptoms of spinal inflammation and examination of the spine are essential. Other important clues may include a history of extra-articular features such as acute iritis or a family history of AS. A further difficulty in diagnosing the patient with AS who presents with small joint synovitis is that sometimes joint erosions, indistinguishable from those seen in RA, are found on radiographs of hands and feet.

Psychogenic rheumatism

Somatisation disorders may also present with symptoms which superficially resemble polyarthritis. In practice, with careful attention to the history, clinical findings and a few selected investigations with normal results, the diagnosis should be clear. The predominant symptom is usually pain more than stiffness, the distribution of pain is likely to be diffuse and not clearly related to joints and there are often widespread multiple tender areas detected on palpating paraspinal and girdle muscles. The typical diurnal variation of symptoms so characteristic of inflammatory disorders is usually absent, but a few patients do complain of generalising morning stiffness which may be a cause of diagnostic confusion. Although some patients may complain of diffuse puffiness, there is a lack of objective joint signs, such as swelling or restriction. If sought, there is likely to be clear evidence of mood and sleep disturbance which is often regarded by the patient as a secondary manifestation of their pain. The importance of non-specific musculoskeletal symptoms as a marker of distress has been highlighted in a recent community study.[25]

Systemic vasculitides

Wegener's granulomatosis, polyarteritis nodosa and Churg Strauss syndrome may present with features mimicking RA and although these conditions are rare, they are important because of their morbidity and mortality. They may present with a prodromal period of low grade symmetrical polyarthritis before erupting into the classic and florid systemic picture. Often however there are extra-articular features which suggest the diagnosis of vasculitis during the prodromal period. These include for example unexplained recurrent sinusitis or otitis media, episcleritis, asthma or pulmonary infiltrates or systemic symptoms such as weight loss and fever. Such features occurring in association with a polyarthritis should broaden the differential diagnosis and lead to further investigations. The identification of antibodies to neutrophil cytoplasmic antigens (c-ANCA) in patients with vasculitis[26–29] raised hopes that serological tests for ANCA would help in the diagnosis of vasculitis; however experience is still limited and these tests should be applied with caution. A further factor confounding diagnosis is that tests for RF are positive in a significant number of patients with vasculitis.

Osteoarthritis

In middle-aged or older patients osteoarthritis (OA) may be confused with RA. Early generalised OA may cause mild morning stiffness of fingers and arthralgia, but careful examination will reveal that the affected joints are mainly DIP, PIP or 1st carpometacarpal joint with sparing of the MCP joints contrasting with the typical pattern found in RA. As the incidence of RA increases with age, not infrequently middle-aged females develop RA against a background of OA. To cause further confusion there is also a less common 'pseudo-rheumatoid' pattern of OA in which swelling and tenderness of the MCPJ of index and middle fingers is found. The distinction from RA is made on the clinical and radiographic findings which reveal osteophytosis and degenerative changes. This pattern of OA is important, particularly in middle-aged males, as it may be the presenting feature of metabolic conditions, notably haemachromatosis and hyperparathyroidism.[30]

ATYPICAL PRESENTATIONS OF RA

A small proportion of patients present with atypical forms of RA which include monoarthritic, polymyalgic and palindromic patterns of joint involvement. Approximately 10 to 20 per cent of RA patients present with an isolated monoarthritis, providing a diagnostic difficulty since they are often seronegative for rheumatoid factor and sometimes only the passage of time reveals the correct diagnosis. Such patients are not infrequently subjected to inappropriate arthroscopy and synovial biopsy, the latter often being reported as showing 'changes compatible with RA'. Unfortunately the histology of rheumatoid synovium is also 'compatible with' other forms of chronic synovitis including psoriatic arthritis, reactive arthritis or ankylosing spondylitis. Radiographs may occasionally be helpful in suggesting alternative diagnoses such as chronic infection, but usually do not contribute to the diagnosis. A major difficulty in the diagnosis of chronic monoarthritis is that it may rarely be due to a serious disorder such as tuberculosis[31] or proliferative villonodular synovitis.[32] Where such diagnoses are being entertained, arthroscopy and biopsy may be very useful and are essential for the diagnosis of tuberculosis. However, if the patient is otherwise healthy, there has been no radiological deterioration in the joint and there are no other clinical clues to suggest serious pathology, it is reasonable to avoid invasive investigations and to manage the patient conservatively.

RA with a 'polymyalgic' onset can also present diagnostic difficulties. These patients complain of symmetrical girdle pain and morning exacerbation of stiffness which may be difficult to distinguish from polymyalgia rheumatica.[33] Features which clearly mitigate against PMR include age under 50 years and a normal or relatively normal erythrocyte sedimentation rate (ESR). PMR is uncommon under the age of 55 and probably never occurs before the age of 50. Also, while a significantly raised ESR or C-reactive protein is a sine qua non for the diagnosis of PMR, these tests may be either normal or raised in RA. Although peripheral joint synovitis may sometimes be a feature of PMR, its presence is more likely to indicate a polyarthritis such as RA. Whether or not synovitis is present, the RF should always be performed to help exclude RA. Some patients, who eventually develop the typical features of RA, at presentation have a syndrome quite undistinguishable from classical PMR.

Finally a small proportion of RA patients present with 'palindromic rheumatism'. Such patients have recurrent acute painful attacks of monoarthritis affecting predominantly medium sized upper limb joints—for example the wrist or elbow—and less frequently the lower limb joints. The attacks build up over a 24 to 48 hour period and then fade over a similar time period. In many patients the syndrome of 'palindromic rheumatism' persists and recurs over long periods of time though in a proportion it evolves into other defined forms of polyarthritis including RA. Patients presenting with 'palindromic rheumatism' should therefore have a rheumatoid factor test included in their routine investigation.

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ECONOMIC EVALUATION OF THE TREATMENT OF RHEUMATOID ARTHRITIS★

Julie A. Ives,† and C. M. Lambert,‡ Western General Hospital, Edinburgh

Because the resources available for health care are limited, those delivering it have a responsibility to ensure that the expenditure represents 'value for money'. Treatment must not only be effective, producing the desired health outcome, but it must also be efficient, that is, producing the desired outcome at least cost. The discipline of health economics enables the systematic appraisal of the costs and benefits of treatment and allows the relative economic efficiency of different medical interventions to be quantified, thus permitting more rational decisions to be made about health care expenditure,

There are two forms of economic efficiency. Allocative efficiency is concerned with the overall apportionment of funding, the issue of whether it is worth achieving a given objective or whether an alternative course of action would yield greater benefit. Quite disparate programmes can be compared, such as whether overall benefit is greater from building a new sewage plant or a new hospital. Operational efficiency, however, starts with the assumption that, in the context of health care, a condition is worth treating and is concerned with the most efficient way of meeting the objective. For example, how can we achieve remission of active rheumatoid arthritis at least cost?

Clearly in this respect a treatment which results in a significantly poorer route to a given outcome than an alternative, for example the conventional treatment, would normally be discounted (Fig 1, line A). However, the situation is not always so clear cut and an economic evaluation can be helpful in making the choice between interventions where the route to the given outcome is only a little better or a little worse than conventional treatment (Fig 1, lines B and C). A cost effectiveness study would make the cost difference explicit and raise the question of whether the increased benefit is worth the increased expenditure.

TYPES OF ECONOMIC ANALYSIS

Once resources have been allocated to health care the technical efficiency with which they are deployed becomes of paramount importance. Value for money can be assessed by four types of economic study, cost-minimisation analysis (CMA), cost–effectiveness analysis (CEA), cost–benefit analysis (CBA) and cost–utility analysis (CUA) (Table 1). If undertaken correctly each identifies costs in the same way but they measure the benefit, or effectiveness of an intervention, in different ways.

In any method of economic analysis it is important to identify, measure and value all the relevant costs and benefits. For example, in a pharmacoeconomic

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†Clinical Research Scientist.
‡Medical Director, Economic and Health Outcomes Research Unit.