Approach to Seronegative Arthritis

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Introduction

Joint pains are quite common in day-to-day practice. The first task of the clinician is to ascertain the exact source of pain by a careful clinical examination. Pain around a joint may be due to bursitis, tendonitis, etc., and not due to arthritis in all cases. The next task is to differentiate arthralgias (joint pains without obvious clinical inflammation) from arthritis (characterised by demonstrable inflammation). Arthralgias are often nonspecific and may be seen in several conditions, like systemic diseases, post-viral arthralgias, hypothyroidism, etc. Arthritis manifests typically with joint swelling and tenderness. Raised temperature and visible redness are usually not seen in chronic inflammatory arthritides. Finally, the clinician would do well to realise that several musculoskeletal diseases resemble each other at the outset, and a definitive diagnosis may not be possible at the first visit. A definite pattern may become discernible only over a prolonged period of observation. In such a situation, symptomatic treatment without a specific label is quite appropriate.

Seronegative arthritis is characterised by the absence of rheumatoid factor (RF). I will first briefly dwell upon RF before embarking on seronegative arthritis.

Rheumatoid factor and seropositive arthritis

The commonly available tests for rheumatoid factor detect IgM (RF is an autoantibody directed against IgG). Detection of IgG or IgA rheumatoid factors is seldom required in clinical practice. Rheumatoid arthritis (RA) is entirely a clinical diagnosis. One can confidently make a diagnosis of RA on clinical grounds even if RF is absent. In fact, only 80-85% of the individuals are seropositive (that is, +ve for rheumatoid factor). Nearly 15-20% are seronegative.

RA is typically bilaterally symmetrical. Asymmetrical or unilateral involvement should arouse suspicion of other arthritides like psoriatic or seronegative spondyloarthropathy.

RA is a polyarthritis. Never diagnose RA in a patient with monoarthritis.

Do not diagnose RA unless hands are involved.

Distal interphalangeal joint involvement is exceedingly uncommon in RA. If DIP joints are involved, suspect psoriatic arthropathy, scleroderma, or osteoarthritis.

Lumbar spine is not involved in RA. The presence of inflammatory low back ache with mono or oligoarticular involvement especially in lower limbs should arouse suspicion of seronegative spondyloarthropathy.

Mere presence of rheumatoid factor in blood is not enough to make a diagnosis of RA.

Once RF is positive in a given patient, it need not be repeated, since it correlates poorly with clinical response to treatment.

Titres of RF do not help in monitoring treatment efficacy.

A negative RF may be repeated 4-6 monthly for the first 2 years of disease, since some patients with RA may take 18-24 months to become seropositive.

Table I: Rheumatoid arthritis and rheumatoid factor: key points.

- RA is entirely a clinical diagnosis. One can confidently make a diagnosis of RA on clinical grounds even if RF is absent. In fact, only 80-85% of the individuals are seropositive (that is, +ve for rheumatoid factor). Nearly 15-20% are seronegative.
- RA is typically bilaterally symmetrical. Asymmetrical or unilateral involvement should arouse suspicion of other arthritides like psoriatic or seronegative spondyloarthropathy.
- RA is a polyarthritis. Never diagnose RA in a patient with monoarthritis.
- Do not diagnose RA unless hands are involved.
- Distal interphalangeal joint involvement is exceedingly uncommon in RA. If DIP joints are involved, suspect psoriatic arthropathy, scleroderma, or osteoarthritis.
- Lumbar spine is not involved in RA. The presence of inflammatory low back ache with mono or oligoarticular involvement especially in lower limbs should arouse suspicion of seronegative spondyloarthropathy.
- Mere presence of rheumatoid factor in blood is not enough to make a diagnosis of RA.
- Once RF is positive in a given patient, it need not be repeated, since it correlates poorly with clinical response to treatment.
- Titres of RF do not help in monitoring treatment efficacy.
- A negative RF may be repeated 4-6 monthly for the first 2 years of disease, since some patients with RA may take 18-24 months to become seropositive.
Table II: Diseases associated with a positive RF.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>• RA</td>
<td>80-85</td>
</tr>
<tr>
<td>• Elderly people</td>
<td>5</td>
</tr>
<tr>
<td>• Other chronic inflammatory rheumatic diseases</td>
<td></td>
</tr>
<tr>
<td>- Primary Sjogren’s syndrome</td>
<td>75-90</td>
</tr>
<tr>
<td>- Mixed cryoglobulinaemia</td>
<td>90-100</td>
</tr>
<tr>
<td>- SLE</td>
<td>20-30</td>
</tr>
<tr>
<td>- Systemic sclerosis</td>
<td>20-30</td>
</tr>
<tr>
<td>- Mixed connective tissue disease</td>
<td>50-60</td>
</tr>
<tr>
<td>• Chronic bacterial infections</td>
<td></td>
</tr>
<tr>
<td>- Subacute bacterial endocarditis</td>
<td>25-50</td>
</tr>
<tr>
<td>• Miscellaneous conditions</td>
<td></td>
</tr>
<tr>
<td>- Sarcoidosis</td>
<td>5-33</td>
</tr>
<tr>
<td>- Interstitial pulmonary fibrosis</td>
<td>10-50</td>
</tr>
<tr>
<td>- Chronic active hepatitis</td>
<td>25-40</td>
</tr>
</tbody>
</table>

Seronegative arthritis

Seronegative arthritis should be differentiated into inflammatory versus non-inflammatory (Figure 1). Inflammatory arthritides, like RA, are characterised by marked morning stiffness (> 30 minutes), pain which improves on gently moving the joint and elevated ESR/CRP. Non-inflammatory arthritides are characterised by mild morning stiffness (< 30 minutes), pain which worsens on joint movement, and normal acute phase response. The important non-inflammatory seronegative arthritides are osteoarthritis and hypothyroidism (Figure 1). Seronegative inflammatory arthritides are divided into monoarthritis (single joint involvement), oligoarthritis (2, 3 or 4 joints affected), and polyarthritis (> 5 joints). The important conditions in each category are listed in Figure 1.

The causes of monoarthritis are listed in Table III. Involvement of a single joint should prompt the clinician to consider crystal arthropathy (like gout), or septic arthritis. A good rule of the thumb is to consider every case of monoarthritis as infection of the joint unless proven otherwise. This is because untreated septic arthritis rapidly results in joint destruction. Hence, overlooking septic arthritis is a serious error. Sometimes, polyarticular diseases like RA begin with single joint involvement. This may cause confusion in diagnosis initially. However, the pattern of disease becomes apparent with time.

Table III: Differential diagnosis of monoarthritis.

- Septic arthritis
- Tuberculous arthritis
- Gout and other crystal deposition diseases
- Seronegative spondyloarthopathy (SpA)
- Tumours
- Trauma
- Haemophilia
- Monoarticular presentation of polyarticular disease

The causes of oligoarthritides are listed in Table IV. It is important to realise that some conditions, like gout, can present as monoarthritis, oligoarthritis, or rarely even as polyarthritis. Similarly, juvenile idiopathic (rheumatoid) arthritis or psoriasis can have oligoarticular or polyarticular involvement. Definitive diagnosis of gout requires crystal identification. Hyperuricaemia alone is not sufficient to make a diagnosis of gout. The seronegative spondyloarthropathies (SpA) constitute the vast majority of oligoarthritides encountered in clinical practice. These conditions (Table V) share several common features which are set out in Table VI. Clinically, SpA should be suspected whenever a young patient (< 40 years) presents, with inflammatory low back pain, and asymmetrical, below waist oligoarthritis, that is, asymmetric involvement of knees or ankles. The majority of cases are associated with HLA-B27. However, it needs to be kept in mind that nearly
5-6% of the healthy north Indian population is HLA-B27 positive.

**Table IV: Common causes of oligoarthritis.**
- Gout
- Juvenile idiopathic (rheumatoid) arthritis
- Psoriasis
- Seronegative spondyloarthropathies (SpA)

**Table V: Seronegative spondyloarthropathies (SpA).**
- Ankylosing spondylitis
- Reactive arthritis (including Reiter’s syndrome)
- Psoriatic spondyloarthropathy
- Inflammatory bowel disease (Enteropathic spondyloarthropathy)
- Juvenile spondyloarthropathy
- Unclassifiable or undifferentiated spondyloarthropathy

**Table VI: Key features of seronegative spondyloarthropathies.**
- Seronegative, that is, rheumatoid factor is absent
- Affect the axial skeleton; inflammatory low back pain is common
- Cardinal feature is involvement of sacroiliac joints
- Peripheral joint involvement is usually asymmetrical, oligoarticular, below waist
- Usually associated with HLA-B27.
- Enthesopathy (pain along tendon insertion sites) is characteristic
- Usual age < 40 years
- Male preponderance

The important seronegative inflammatory polyarthritides are listed in Table VII. The commonest is seronegative RA. The presence of extra-articular features like fever, oral ulcers, malar rash, and alopecia, should alert the clinician to the presence of lupus. The arthritis of lupus may be clinically indistinguishable from RA. However, typically lupus arthritis is non-erosive, while RA may show erosions. The presence of prominent Raynaud’s phenomenon in a patient with joint pains should alert the physician to the possibility of scleroderma, while skin lesions of psoriasis suggest a diagnosis of psoriatic arthropathy. History of bloody diarrhoea may be a pointer towards enteropathic arthritis. Adult onset Still’s disease is, by and large, a diagnosis of exclusion.

**Table VII: Seronegative inflammatory polyarthritides.**
- Seronegative RA
- Psoriatic arthropathy
- SLE
- Scleroderma
- Juvenile idiopathic arthritis
- Adult onset Still’s disease
- Inflammatory bowel disease

A thorough history and good physical examination enable the clinician to arrive at a diagnosis in most instances. Investigations are meant to be supplements to and not substitutes for clinical judgement.

**References**

**ANNOUNCEMENT**

**XIV-RAJ APICON-2003**
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