SERONEGATIVE SPONDYLOARTHRopathies
- A REVIEW
PART I: CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS

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ABSTRACT

The seronegative spondyloarthropathies comprise a group of non-rheumatoid disorders with similar clinical, laboratory and genetic features. Recognition of new clinical features has supported the notion that they all form part of a clinical spectrum. These features and the classification of the seronegative spondyloarthropathies are discussed in the review.

The seronegative spondyloarthropathies consist of a group of non-rheumatoid disorders with similar clinical, laboratory and genetic features. Several of these disorders have salient characteristics that enable full recognition of the individual syndrome.

It is not invariably possible to make a clear distinction between the various clinical entities, lending support to the notion that they should be considered as part of a clinical spectrum [1].

These disorders [2] are characterised by (Table 1)

1. Absence of high titre IgM rheumatoid factor.

High titres of rheumatoid factor have been correlated with severe progressive rheumatoid arthritis (RA), but low titres are found in many connective tissue diseases, chronic infections and 5% of normal individuals. The frequency of rheumatoid factor increases with age [3].

2. Sacroiliitis and/or spinal involvement.

The hallmark of ankylosing spondylitis (AS) is bilateral, symmetric sacroiliitis. An asymmetric or unilateral distribution may be evident in the early disease phase. In patients with psoriatic arthritis or Reiter's disease, the pattern of sacroiliitis is most often bilateral and symmetric, but asymmetric or unilateral involvement is seen more often than in AS.

In the spine, AS may result in abnormalities of the discovertebral junction, the apophyseal and costovertebral joints, posterior and anterior ligaments and the atlantoaxial articulations. Changes are usually first seen at the thoracolumbar junction. Osteitis at the discovertebral junction, occurring centrally or at the vertebral corners, is an important early sign of AS. Erosion of the vertebral edges creates a squared contour and with healing, reactive sclerosis results.

Studies of the relationship between sacroiliitis and ascending spinal disease suggest that these conditions form part of the same disease spectrum with progression from one to the other depending mainly on disease duration.

TABLE I

Characteristics of the Spondyloarthropathies

1. Absence of high-titre IgM Rheumatoid Factor.
2. Sacroiliitis/Spinal involvement.
3. Peripheral inflammatory arthropathy.
5. Extra-articular involvement.

Psoriatic spondylitis and Reiter's disease produce identical findings in the spine. In Reiter's disease however, the incidence and extent of spinal disease is often less than in psoriatic spondylitis or AS. Vertebral squaring and discovertebral osteitis are relatively uncommon findings in psoriatic and Reiter's spondylitis. Spinal changes classically involve the lower thoracic and upper lumbar segments and segmental spinal involvement is common [4].

Although AS is historically regarded as a male disease, it is increasingly being recognised in females. There does not appear to be any difference in the spinal symptoms, chest expansion, peripheral arthritis and extra-articular features between males and females with AS (Figure 1).
Although males tend to have more severe axial disease and more pronounced radiological changes at an earlier stage than women, the overall pattern of clinical disease is similar in both sexes [5-7].

Chest pain aggravated by coughing or sneezing due to involvement of costovertebral and costotransverse joints is now recognised to be a feature of AS and may be present in up to 63% of patients. The chest pain has been shown to predate the diagnosis of AS in 18% of patients and is often associated with tenderness over the sternocostal or costochondral junction [8].

A disorder that may present with similar spinal changes is Diffuse Idiopathic Skeletal Hyperostosis (DISH). This disorder is characterised by the formation of large osteophytes and enthesopathy. It is generally seen in patients over the age of 50. Patients may be asymptomatic or complain of back stiffness.

The radiographic criteria for diagnosis require the absence of extensive degenerative disc disease or inflammatory changes in the sacroiliac and apophyseal joints (Figure 2). A characteristic extraspinal manifestation of DISH is extensive enthesopathy with prominent calcification and ossification of tendons and ligaments [9].

3. Peripheral inflammatory arthropathy

Involvement of peripheral joints in AS is often mild and transient. The most common extra-axial joints involved are the hip and the glenohumeral joint. Prominent erosive and destructive changes may occur and the hip, in particular, may be an important source of clinical disability. Radiographic findings include osteophytosis, subchondral cysts and concentric joint space narrowing [10].

Psoriatic arthritis demonstrates a wide variety of patterns of peripheral joint disease. These include an asymmetric oligoarthritis (70% of cases), a symmetrical polyarthritis similar to RA (15%), predominant distal interphalangeal involvement (<5%) and a mutilating arthritis (<5%). In less than 5% of patients with psoriatic arthritis, AS is the predominant feature.

This classification has been challenged, the main argument concerning the pattern of the peripheral arthritis found. A recent study [11] suggests that the majority of subjects with psoriatic peripheral arthritis have a symmetrical polyarthritis resembling that of RA and most present with this pattern of disease.

Fusion of the interphalangeal joints is a useful marker of psoriatic arthritis, as this is rarely seen in AS, Reiter’s disease or RA.

The peripheral arthritis of psoriasis may result in a radiographic appearance similar to that of inflammatory (erosive) osteoarthritis.

This disorder is commonly seen in elderly women and tends to involve the DIP and PIP joints, and is associated with central, rather than marginal, erosions in combination with osteophyte formation. Periarticular osteoporosis is usually absent and bony ankylosis of the interphalangeal joints occurs [12].

The peripheral arthritis of Reiter’s disease/Reactive arthritis is characterised by asymmetric involvement of the

FIG. I Classical appearance of a male patient with AS. Note the marked kyphosis.

FIG. II Plain X-ray of early Forrestier’s disease showing large osteophytes with normal sacro-iliac joints.
axial or large weight-bearing joints. The knees and ankles are most often involved. Spondylosis with prominent enthesitis is often a feature. Radiographic findings are similar to those of psoriatic arthritis, however, significant destruction or deformity and bony ankylosis is less than in psoriatic arthritis. There is also less cervical spine and upper extremity involvement.

4. Familial aggregation

The occurrence of AS has been recognised in twins, brothers, fathers, mothers, and other relatives of affected individuals [13]. The different disease expressions of relatives of patients with AS, Psoriatic arthritis or Reiter's disease is also well recognised, and considered in greater detail later.

5. Extra-articular involvement:

- Iritis and conjunctivitis
- Urethritis
- Mucous membrane ulcers
- Skin rash

Cardiovascular involvement in the form of myocardial dysfunction, cardiac valvular lesions and conduction disturbances is being increasingly recognised in AS and the related spondyloarthropathies [14-16].

6. Enthesopathy (Figure 3)

This is defined as inflammation at the ligament-bone junction [17]. Favoured sites of involvement include the ischial tuberosities, iliac crests, femoral trochanters and plantar aspect of the calcaneus. Inflammation results in subtendinous/subligamentous erosion, which is followed by reactive sclerosis and heterotopic ossification [18].

The clinical entities included in the seronegative spondyloarthropathy group are [19]:

1. Ankylosing Spondylitis
2. Psoriatic Arthropathy
3. Reiter's Disease/Reactive Arthritis

**ENTHESITIS**

![Diagram illustrating the definition of an enthesis.](image)

4. **Inflammatory Bowel Disease** (Ulcereative colitis, Crohn's disease, Whipple's disease)

5. **Juvenile Chronic Arthritis (JCA).**

JCA is defined as the occurrence of inflammatory arthritis before the age of sixteen [20]. The existence of several clinical forms of JCA is well recognised [21]. Pauciarticular and polyarticular JCA are immunologically distinct with persistent pauciarticular disease developing preferentially in patients having HLA-DRw8 while in the polyarticular form of JCA HLA- DPw3 is the major factor for susceptibility [22].

Polyarticular JCA has a clinical spectrum similar to adult RA. Systemic onset JCA is characterised by fever, an evanescent rash, variable arthritis and a marked acute phase response.

Pauciarticular JCA has a clinical presentation similar to the seronegative spondyloarthropathies with lower limb arthritis, enthesitis, acute uveitis and eventual sacroiliitis in a number of cases [23].

The classification of Behcet's Syndrome (BS) is still controversial. Some groups still suggest that it should be grouped with the seronegative spondyloarthropathies because of its involvement of mucous membranes, eyes, gastro-intestinal and genito-urinary tracts, and joints. However, in view of the clear difference in these lesions as well as the different HLA spectrum, the current thinking is that BS should be classified with the vasculitides. This is in keeping with the histological finding of both arterial and venous vasculitis [24].

The term "Reactive Arthritis" was introduced by Ahvonen in 1969, and can be defined as a "Syndrome characterised by nonpurulent joint inflammation following an infection elsewhere in the body" [25].

Epidemiological evidence accumulated from different sources strongly favours a casual relationship between gastro-intestinal infections with Shigella, Salmonella, Yersinia, Campylobacter and genito-urinary infection with Chlamydia and the subsequent development of arthritis.

Most patients with reactive arthritis are young adults, aged 20-40 years [26]. The arthritis usually appears up to three weeks following the onset of infectious symptoms. The initial infection is often mild and may be asymptomatic in about 10% of patients [27].

The severity of the triggering infection does not bear any clear correlation with the development of arthritis. Sexually acquired reactive arthritis usually follows urethritis or cervicitis but the triggering infection cannot always be identified [28]. In women, urogenital involvement may precede joint symptoms by up to five years [29].

The time lag between infection and the onset of arthritis is the main difficulty in identifying the aetiology of the triggering infection.
By the time the diagnosis is suspected, microbiological culture, whether in urine, blood or stool is usually negative. Thus, the diagnosis is usually serological [30].

References

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