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Ankylosing Spondylitis and Other Seronegative Arthritis

Balaji Zacharia and Antony Roy

Abstract

Spondyloarthropathies are a group of disorders having some common features. They are characterised by inflammation of the attachment of tendons known as enthesitis. They are common in males. There is a familial occurrence. There is an association with HLA-B 27. Rheumatoid factor will be negative. Axial skeleton involvement in the form of sacroiliitis or spondylitis is common. The common conditions include ankylosing spondylitis, Reiter's disease, psoriatic arthritis, enteropathic arthritis and reactive arthritis. In this chapter we are going to describe the clinical features, evaluation and management of common spondyloarthropathies.

Keywords: spondyloarthropathies, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, psoriatic arthritis

1. Introduction

Spondyloarthropathies are a group of disorders having common clinical features and are characterised by inflammation of the attachment of tendons known as enthesitis. They are common in males and show familial inheritance patterns. The HLA-B 27 allele is frequently associated with these disorders. A rheumatoid factor assay will be negative (seronegative spondyloarthropathy). Axial skeleton involvement in the form of sacroiliitis or spondylitis is common. The common conditions include ankylosing spondylitis, Reiter's disease, psoriatic arthritis, enteropathic arthritis and reactive arthritis [1, 2]. In this chapter we describe the classification, clinical features, evaluation and management of common spondyloarthropathies.

2. Classification

A broad clinical classification of spondyloarthropathies into those having a primary axial involvement, those with a predominant peripheral involvement, and those with a hybrid form of affliction, although easier clinical practice, is difficult to reproduce with uniformity. The current favourite diagnostic criteria, The modified New York criteria for AS is heavily dependent on axial spine affliction and recognises advanced structural damage thus reducing the importance of early extra spinal manifestations, serological evidence and genetic predisposition. There is no

emphasis on detection of early radiological manifestations by more informative imaging techniques like magnetic resonance scanning. Inflammatory back pain, the leading clinical symptom of spinal and sacroiliac affliction has been defined by many criteria although its diagnostic significance has not been completely understood and the sensitivity and specificity offered by it is low. It is efficient in diagnosing definite cases although a classification of disease based on it leaves much confusion. The Assessment of SpondyloArthritis International Society axial spondyloarthritis criteria (axSpA) allows for earlier detection of disease thus facilitating earlier disease modification and is more comparable across studies. The focus of treatment in spondyloarthropathies has shifted on to earlier diagnosis and treatment. Magnetic resonance imaging and specific serological tests such as the HLA-B 27 form an essential component of this strategy. In 2011 the ASAS described the peripheral spondyloarthritis criteria specially aimed at the cohort of patients with no or non-specific back pain but with predominant peripheral manifestations [3–5].

3. Ankylosing spondylitis (AS)

This is the prototype disease among spondyloarthropathies. It is also known as Marie-Strumpell disease or Von Bechterew disease. The exact aetiology is unknown. It mainly involves spine and major joints like hip and knee. Sacroiliitis is one of the cardinal features of this disease. It usually affects males in the second or third decade of life. The male to female ratio is 3:1.

There is a striking correlation between AS and HLA-B27 antigen. The disease occurs more frequently in Caucasians where HLA-B27 prevalence is higher as compared to African Americans or Africans of unmixed ancestry. About 1–2% of adults inheriting HLA-B2 antigen have ankylosing spondylitis. In families of patients with AS there is 10–20% prevalence of this antigen. There is no direct causative relationship between HLA-B27 antigen and AS. There is a strong association between AS and inflammatory bowel diseases like ulcerative colitis and Crohn's disease. Both genetic and environmental factors play a role in the pathogenesis of ankylosing spondylitis [6].

3.1 Pathology and pathogenesis

Sacroiliac inflammation is the earliest feature of AS with inflammatory granulation tissue eroding the sacroiliac joint. The inner and thinner iliac cartilage is eroded before the thicker outer sacral sided cartilage. This leads to fibrocartilage tissue replacing the joint space followed by bony ankylosis of sacroiliac joints. There is diffuse osteoporosis of the vertebrae. The inflammation starts at the junction of the intervertebral disc and body. Inflammation and erosion proceeds at the bone disc interface and new bone formation occurs from the edges of the annulus fibrosus known as syndesmophytes. They grow vertically upwards and bridge the adjacent vertebrae producing bamboo spine appearance in radiograph. Early on, inflammation at the bone disc interface produces corner shining sign and later erosion produces squaring of vertebrae. Arthritis of apophyseal joint leads to erosion and later ankylosis of the same. Inflammation and erosion at the sites of attachment of ligaments and tendons are common. Enthesitis followed by calcification is common in the axial skeleton. Unlike in rheumatoid arthritis destruction of central cartilage due to granulation and pannus in peripheral joints can occur in AS. There can be synovitis in peripheral joints.

Extra articular involvement like recurrent uveitis, aortic regurgitation, inflammatory lesions of colon and ileocecal valve and IgA nephropathy are seen in some cases [6, 7].

The exact mechanism of pathogenesis is unknown. It is thought that the destruction is mediated through immunological mechanisms. The elevated levels of inflammatory reactants, Ig A levels in serum and histology suggest inflammation in AS. The exact environmental trigger is not yet identified although elevated levels of antibodies to *Klebsiella pneumoniae* are seen in AS patients. There is no causative association between ankylosing spondylitis and HLA-B27 [8, 9].

3.2 Clinical features

The disease is common in males and in the second and third decade of life. The common presentation in majority of patients is dull aching low back pain which is progressive. There is morning stiffness lasting for few hours and decreased by activity. Pain increasing with rest and improving with exercise is a characteristic feature. Nocturnal exacerbation of pain awakening the patients making them move around is also common. Exacerbations and remissions of symptoms are also common. The enthesitis produces pain in the costochondral junction, greater tuberosity, tibial tuberosity and spinous processes. In some patients the presenting symptom is intractable plantar fasciitis. Neck pain and involvement of cervical spine is late. Sometimes, patients present with features of arthritis in hip or shoulder. Peripheral asymmetrical joint arthritis is rarely seen. Constitutional symptoms like fever, anorexia, weight loss and night sweats can occur rarely.

The common extra articular involvement is ophthalmic. It is usually uni-ocular uveitis. Occasionally it precedes low back symptoms. Red eye, pain, photophobia and increased lacrimation are common. Aortic regurgitation is seen in some patients and can lead to congestive cardiac failure. AS may be associated with inflammatory bowel disease in many patients [8–10].

Tenderness can be elicited over sacroiliac joints, spinous process and areas of enthesitis. The most common feature is loss of mobility of the spine. It is partially due to bony ankylosis and partially due to paraspinal muscle spasms. Forward flexion, lateral rotation and extension of spine are limited. There is loss of lumbar lordosis, increased thoracic kyphosis, flexion deformity of cervical spine flexion deformity of knee. Later this leads to stooping forward posture. This can be demonstrated by occipital wall test. The decreased excursion of lumbar spine movement can be demonstrated by using modified Schober's test. Costovertebral joint involvement can be detected by decreased chest expansion. Sacroiliitis is characterised by local tenderness. Sacroiliac stress test like FABER test, pump handle test can be done though not specific. There can be features of arthritis with ankylosis of hip joints and shoulder. Peripheral joints involvement needs to be evaluated in all cases [8–10].

Earlier onset of disease signals a poor prognosis. They will have severe arthritis of hip. Women have lesser involvement of axial skeleton, mostly isolated involvement of cervical spine and peripheral joints. Due to spinal osteoporosis there can be fractures of spine even with minor trauma. It is common in cervical spine leading to quadriplegia. This is one of the cause of death in AS. There are reports of pulmonary fibrosis, cardiac conduction defects and chronic prostatitis in long standing AS [10, 11].

Restrictive lung disease due to bilateral pulmonary fibrosis can occur. Superadded aspergillosis may mimic tuberculosis. Insertional tendinitis of costosternal and costovertebral muscles leads to pleuritis. Chest expansion is compromised due to fusion of costovertebral joints. There is a threefold increase in risk of death due to respiratory causes in AS patients than in normal people [10, 11].

3.3 Investigations

There is no diagnostic investigation for AS. In the active stage of disease ESR and serum CRP levels are elevated. In severe disease serum alkaline phosphatase will

be elevated. Occasionally normocytic normochromic anaemia is associated. There is an elevated IgA level in most cases. HLA-B27 will be elevated. Synovial fluid examination is usually inconclusive. Rheumatoid factor and antinuclear antibodies will be uniformly absent. Pulmonary function tests show reduced vital capacity and increased residual capacity.

Radiograph of the sacroiliac joints shows bilateral involvement. The initial stage is characterised by blurring of the subchondral bone followed by erosion and sclerosis. Progressive erosion produces pseudo widening of the joints. Later progressive bony ankylosis of bilateral sacroiliac joints is seen. These changes are detected by computerised tomography and MRI at an earlier stage than plain radiograph [12].

In the spine there is diffuse osteoporosis. The initial stages show reactive osteitis at the corners of vertebrae producing corner shining sign on lateral view. Later erosion of the corner area produces squaring of the vertebrae. Syndesmophytes growing vertically from the margins of intervertebral disc bridge the adjacent vertebrae and lead to the typical bamboo spine appearance. Lumbar lordosis is lost and dorsal kyphosis is exaggerated.

Articular erosion in the hip leads to features of arthritis and sometimes protrusio acetabuli, later progressing to bony ankylosis. Even though majority of patients have some functional impairment they can lead a fairly normal life [12, 13].

3.4 Diagnosis and differential diagnosis

The most common presenting symptom of AS is inflammatory back pain characterised by pain low back of more than 3 months duration, pain aggregated with inactivity and relieved with activity, presence of morning stiffness and insidious onset in younger patients below the age of 40. But it will be difficult to diagnose AS early before the development of sacroiliitis or spinal deformities. It has been shown that people positive for HLA-B27 developing sacroiliitis at a later date. Because of these difficulties a criteria was developed for the diagnosis of AS. The modified New York criteria consist of (1) history of inflammatory back pain, (2) reduced range of movement of lumbar spine both in frontal and sagittal planes, (3) reduced chest expansion, (4) radiographic evidence of sacroiliitis. The criteria suggest that the presence of radiographic sacroiliitis with any other criteria can make a diagnosis of ankylosing spondylitis.

There are a few conditions which can mimic AS. Diffuse idiopathic skeletal hyperostosis (DISH) is one differential diagnosis but this is seen in elderly usually calcification is unilateral on the right side, intervertebral spaces are maintained. Radiogram shows ossified anterior spinal ligament as flowing wax. Fluorosis is another disease but this is usually endemic to certain areas and calcification of sacroiliac and sacrotuberous and other ligamentous calcifications are characteristics. Ochronosis and hemochromatosis can produce intervertebral disc calcification but can be differentiated from AS by other features [14, 15].

3.5 Treatment

There is no medical cure for ankylosing spondylitis. Treatment aims to maintain a functional posture and preserve joint mobility. Exercise can improve and preserve mobility. Swimming and yoga are also helpful. In the active stages NSAIDs especially indomethacin is very useful. Intra-lesional and intra-articular glucocorticoid injections are useful for symptomatic relief of enthesitis or peripheral joint arthritis. Guided glucocorticoid injections are also useful for the relief of sacroiliitis. Sulphasalazine is useful for the long term control of peripheral joint arthritis. Peripheral joint symptoms can also be controlled using methotrexate.

The most common surgical treatment is for hip arthritis. Total hip replacements can improve the pain and joint stiffness. Usually hip involvement produces flexion deformity which leads to flexion of knee. Total hip replacement can improve the gait and posture of patients [14, 15].

A fixed kyphotic deformity at the cervicothoracic junction can lead to chin on chest deformity. This is a rare and disabling condition. A posterior cervicothoracic extension osteotomy can be done for this deformity. It helps in restoration of head and neck posture, relieves pain and improves function. Severe kyphotic deformity of dorsal spine can produce pain and inability to stand straight. This can be managed by an extension osteotomy like Watson Jones osteotomy [16–18].

Mydriatics and local glucocorticoid administration are indicated for iritis. Aortic valve replacement may be needed for aortic valve insufficiency and pacemaker for conduction defects [18].

4. Other spondyloarthropathies

4.1 Reactive arthritis or Reiter's syndrome

It is an acute nonpurulent arthritis occurring following an episode of enteric or urogenital infection in HLA-B27 positive people. Formerly the classical triad of urethritis, arthritis and conjunctivitis was known as Reiter's syndrome. Although Reiter's syndrome is one among the reactive arthritis this term is not used currently. All spondyloarthropathies occurring following urogenital or enteric infections are termed reactive arthritis even if all classical features of Reiter's syndrome are not present. *Shigella*, *Salmonella*, *Yersinia* and *Campylobacter* are the common organisms that cause enteric infection associated with reactive arthritis. *Chlamydia trachomatis* is the commonest urogenital infection leading to reactive arthritis. When reactive arthritis occur following a sexually transmitted urogenital infection it is termed as Sexually transmitted associated reactive arthritis (SARS), and when occur following gut related infections called Gut associated reactive arthritis (GARS). There is no gender predilection and occurrence is equal in males and females. Although it can occur at any age, commonly affected are individuals of the age group of 20 to 40 years. Similar to ankylosing spondylitis, there is a close association between HLA-B27 and reactive arthritis [19].

Pathology is similar to other inflammatory arthritis. Enthesitis is also common. Keratoderma blenorrhagica is a skin condition associated with reactive arthritis especially with urogenital infections. The exact triggering mechanism for the pathogenesis of reactive arthritis is unknown. There are reports of acute nonpurulent arthritis associated with bacterial, viral and even parasitic infections. Like in ankylosing spondylitis it is mediated through immunological mechanisms. There is persistence of organism in the inflamed synovium for prolonged duration although not demonstrated in blood. The role of HLA-B27 also remains unclear.

4.2 Clinical features

The clinical features can range from mild mono articular involvement to asymmetrical poly articular arthritis. Most patients will give a history of antecedent infection either in the GI tract or urogenital region. Sometimes, there is a history of sexual promiscuity. In males, urethritis or prostatitis and in females cervicitis or salpingitis may be present though asymptomatic. Unlike ankylosing spondylitis, constitutional symptoms like fatigue, malaise, fever are common in reactive arthritis. The arthritis typically involves the lower limb joints. Knee, ankle, subtalar,

metatarsophalangeal joints and inter-phalangeal joints are commonly involved. There is asymmetrical involvement and usually migrates from one joint to another over a period. Wrist and fingers can also be involved. Painful joints with tense effusion are common especially in large joints like knee. Dactylitis with sausage digits can occur in single or multiple fingers. Enthesitis producing symptoms of insertional tendo achilles tendinitis and plantar fasciitis can be seen. Low back pain due to sacroiliitis, enthesitis is also seen [20].

Extra articular lesions like conjunctivitis and severe uveitis can cause blindness in certain patients with reactive arthritis. Vesicular and hyperkeratotic lesions seen in hand and foot are called Keratoderma blenorrhagica. Circinate balanitis of glans penis is also described. Like in ankylosing spondylitis aortic regurgitation, cardiac conduction defects and pulmonary involvement can rarely occur [21].

4.3 Investigations

In the acute phase there will be elevated ESR and CRP. Synovial fluid analysis is inconclusive. Occasionally there is a marked elevation of antibodies to salmonella, chlamydia and yersinia indicating recent infections with these organisms.

Radiograph will be normal in early cases. Later on, peri-articular osteoporosis develops in chronic cases followed by juxtaarticular erosions and loss of joint space. New bone formation due to periostitis can occur. Spur formation at the attachments of tendons are also seen. Sacroiliitis and spondylitis occur very late and are uncommon. Sacroiliitis is unilateral and asymmetrical. Unlike in ankylosing spondylitis the spondylitis may not show an ascending pattern and it can involve any level. The syndesmophytes may be coarse and nonmarginal arising from the middle of vertebrae. Spinal fusion is very rare [21, 22].

4.4 Diagnosis and differential diagnosis

Diagnosis is based on clinical examination as there is no confirmatory laboratory test available. A careful history of recent infection in the gut and urogenital tract is to be elicited. Careful examination of genitalia, eye, skin, nail and mucous membranes must be done. In doubtful cases HLA-B27 testing can be done [23].

The most common differential diagnosis is gonococcal arthritis. But it involves both lower and upper limbs equally. Low back pain is not seen in gonococcal arthritis. Characteristic vesicular skin lesions are common. Culturing gonococci from blood, skin lesion or synovium establishes the diagnosis. Psoriatic arthritis is another differential diagnosis [24].

Undifferentiated spondyloarthropathies can present like reactive arthritis. They may present with isolated arthritis involving knee, ankle or dactylitis or enthesitis like plantar fasciitis and insertional tendo achilles tendinitis. They may not meet the diagnostic characteristic of other classical spondyloarthropathies. Approximately half of patients with undifferentiated spondyloarthropathies are HLA-B27 positive [23, 24].

4.5 Treatment

Most patients with reactive arthritis respond well to NSAIDs for symptomatic relief. Indomethacin 75–150 mg in divided doses is the initial treatment of choice. Sulphasalazine up to 3 g/day may be helpful especially patients not responding to NSAIDs. Immunosuppressive agents such as azathioprine 1–2 mg/kg per day and methotrexate 7.5–15 mg per week are useful. Tendinitis and enthesitis can be treated with intralesional glucocorticoid injections. Uveitis may require aggressive treatment with glucocorticoid to prevent blindness [21, 23].

5. Psoriatic arthritis

Since the association between HLA-B27 and psoriatic spondylitis (60%) is less when compared to AS (94%) it is included in spondyloarthropathies. About 2% of individuals having psoriasis develop arthritis. Peripheral arthritis is common than axial disease. In majority of patients skin lesions predate arthritis. But in one fourth of cases the skin lesions appear simultaneously or arthritis predate skin lesions. In such cases there may be a family history of psoriasis. Nail changes like ridging, pitting and onycholysis are common in psoriatic arthritis. Though psoriatic distal inter-phalangeal joint arthritis is common in males incidence is similar in both sexes. There are many forms of psoriatic arthritis [25].

1. Oligoarticular disease (70%): it is the most common type of psoriatic arthritis. Asymmetrical arthritis involving the lower limb joints is common. It can involve small joints of fingers. Both distal and proximal inter-phalangeal joints are involved- sausage fingers. Lack of distal inter-phalangeal joint involvement helps to differentiate it from rheumatoid arthritis. Nail changes are frequent in fingers having distal inter-phalangeal involvement.
2. Symmetrical polyarthritis (15%): it may be indistinguishable from rheumatoid arthritis. But presence of rheumatoid nodules and distal inter-phalangeal joint involvement and positive rheumatoid factor helps to distinguish it from rheumatoid arthritis.
3. Arthritis mutilans (5–10%): it is a severe destructive asymmetrical arthritis. It is usually seen in severe form of psoriasis. It is associated with sacroiliitis and spondylitis.
4. Psoriatic spondylitis (25%): it is strongly associated with HLA-B27 (60%). Majority of cases are asymptomatic. Asymmetrical sacroiliitis is common. Spondylitis without sacroiliitis producing florid syndesmophyte formation is common in psoriasis.

Features like distal inter-phalangeal joint involvement, absent peri articular osteoporosis, periostitis, ankylosis, pencil in cup deformities of DIP joints and axial skeleton involvement in radiograph help to differentiate it from rheumatoid arthritis. Sometimes, concomitant gouty arthritis can be seen even in premenopausal women due to high skin cell turnover [26, 27].

5.1 Treatment

Majority of cases are oligoarticular and mild and have good prognosis. NSAIDS are the mainstay of symptomatic treatment. Intra-articular glucocorticoid injections are helpful in oligoarticular disease. Methotrexate and azathioprine are useful for long term control of both skin and arthritic lesions. Antimalarial and systemic steroids must be avoided for the fear of exacerbation of skin lesions [28].

6. Enteropathic arthritis

Seronegative spondyloarthropathies can occur in association with inflammatory bowel disorders (IBD). They are twice commonly associated with Crohn's disease than ulcerative colitis. Two forms of peripheral arthritis are described.

Type 1: it is strongly associated with extra intestinal manifestations of IBD. It is usually pauciarticular and is seen during relapses of IBD. It is acute and self-limiting.

Type 2: more than five joints are involved. It runs a chronic course lasting for years independent of the IBD. Uveitis can occur but other extra intestinal manifestations are rare.

Extra articular manifestations like erythema nodosum, pyoderma gangrenosum, aphthous stomatitis can occur. Exact pathogenesis of enteropathic arthritis is not known. Increased gut permeability leading to entry of bacilli from gut into general circulation and immune mediated mechanism is one proposed theory [29, 30].

6.1 Treatment

There will be intolerance to NSAIDs due to gastrointestinal involvement. Hence simple analgesics are used. Intra-articular glucocorticoid injections are useful. Sulfasalazine is useful for the control of both arthritis and gut disease. Systemic corticosteroids, methotrexate and azathioprine are also used [30, 31].

6.2 Biological DMARDs in spondyloarthropathies

Treatment with biological agents is used in patients who fail to respond to NSAIDs. It should be started at an early stage to prevent progression. Tumour necrosis factor alpha inhibitors are the commonest drugs used. They prevent cartilage damage in peripheral joints than in axial joints. These drugs reduce the radiographic progression of disease in AS when administered early. Highest response to these drugs occurred in psoriatic arthritis patients with elevated CRP levels. Due to fear of reactivation it is always better to screen for the presence of latent tuberculosis or hepatic viral diseases [30]. In addition to biological agents the ASAS recommends a single local corticosteroid injection in cases of peripheral spondyloarthritis.

7. Tumour necrosis factor alpha inhibitors

Etanercept, infliximab, adalimumab, golimumab, certolizumab are the common TNF alpha inhibitors used. Infliximab is used intravenously and the others are administered subcutaneously. They are effective for spondyloarthropathies and psoriatic arthritis which are not controlled by NSAIDs and traditional DMARDs. Certolizumab, a recent drug is effective in reducing the symptoms and axial involvement in AS. Infliximab, adalimumab, golimumab are used in IBD to treat both bowel and joint diseases. Etanercept is useful in controlling axial skeleton involvement but its effect on enteric disease is limited. Infliximab and adalimumab used in AS have shown to decrease the rate of recurrences. Golimumab is found to be effective in refractory uveitis associated with spondyloarthropathies. TNF-alpha inhibitors like infliximab, adalimumab, golimumab, and etanercept are very efficient in treating the skin and nail lesions in psoriasis though exacerbations of lesions can occur rarely with TNF alpha inhibitors. TNF alpha inhibitors decrease cardiovascular manifestations. In AS, the overall treatment with biological DMARDs shows only partial remission or low disease activity [32–34].

Interleukin-6 receptor inhibitors like Tocilizumab and Sarilumab are found to be not effective in the treatment of spondyloarthropathies by various trials. A short-term study involving 30 patients with AS treated using Secukinumab showed its clinical efficacy but need to be confirmed by long term RCTS. Ustekinumab, a fully human monoclonal antibody against a common subunit of IL12 and IL 23, is well tolerated and found to be effective in AS and psoriatic arthritis [35].

8. Current consensus and the way forward

The 2016 update on Assessment of SpondyloArthritis international Society (ASAS)-European league against rheumatism (EULAR) recommendations provide guidance on the management of patients with axial spondyloarthritis. A total of five broad principles of management and treatment recommendations have been put forward. They are precise guidelines to treat patients with axial spondyloarthropathies broadly incorporating therapeutic and diagnostic concerns [36].

9. Conclusion

Spondyloarthropathies are a group of conditions having some common overlapping clinical features. They are common in HLA-B27 antigen positive individuals. There is no conclusive investigation for these conditions hence differentiation is difficult at least in the early stages. For most of the cases only symptomatic treatments are available. Further research is needed for early detection and accurate treatment of these conditions.

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