Review

Spondyloarthritis: not only enthesitis

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ABSTRACT

Spondyloarthritis represents a heterogeneous group of inflammatory diseases that share common genetic, clinical and radiological features. Those diseases are characterised by inflammation in the spine and in the peripheral joints. Enthesitis is considered a pathological hallmark of the spondyloarthritis group of conditions but there are also many other relevant clinical manifestations. The aim of this article is to present an overview on articular and extra-articular manifestations and comorbidities associated with spondyloarthritis.

Introduction

Spondyloarthritis (SpA) is a complex condition with a wide range of clinical manifestations, laboratory abnormalities and imaging features. Genetically, it can be associated with the major Histocompatibility Complex Class 1 Antigen HLA-B 27 (1, 2). HLA B27 positivity rate was 6.9% in healthy controls and 75% in SpA patients (3). The risk of developing SpA in patients with HLA B 27 positivity is from 2 to 10% (1, 2). SpA is an inflammatory condition in which both peripheral and axial joints might be involved. The majority of people with this disease have either psoriatic arthritis (PsA) or axial SpA (axSpA), which includes AS. Other subcategories are enteropathic SpA, associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis), or reactive arthritis, with an occurrence in people with gastrointestinal or genitourinary infections, and undifferentiated SpA that does not meet the diagnosis criteria of the other aforementioned subgroups (4). More recently, the Assessment of Spondyloarthritis International Society (ASAS) has proposed a classification into axial and peripheral disease. Peripheral disease shares several articular manifestations (peripheral arthritis, enthesitis, dactylitis), and extra-articular features (uveitis, psoriasis, and inflammatory bowel diseases) (4). Peripheral and axSpa are characterised by involvement of the spine and sacroiliac joints. In both diseases the lack of pathognomonic factors and laboratory tests may delay the diagnosis. Especially in axSpA, the average delay in diagnosis is estimated to be from 8 to 11 years (5). New studies will be needed for a more complete knowledge of the disease that will allow an early diagnosis, preventing the onset of severe disability.

Physiopathology

The proinflammatory cytokines, such as interleukins (IL) IL-23, IL-17, IL-1 and tumour necrosis factor-α (TNF-α), play an important part in disease pathogenesis (6).

In particular, many recent studies have underlined the role of IL -7 and IL-23 (7-9). Genetic evidence links the IL-23-IL-17 pathway to inflammation in SpA. Also the results of research on animal models confirm the crucial role of these cytokines (10). In the study by Sherlock *et al*., it has been shown that mice that overexpress IL-23 develop enthesitis and peripheral arthritis (11).

In these animal models IL-23 stimulates the production of IL-17 A, IL-22, and IL 17F through the activation of T cells in entheses.

Moreover, Utriainen *et al*. have shown in transgenic HLAB27 positive rats that CD4+ cells produce IL-17. (12) Ebihara *et al*. have also demonstrated that the use of IL-17 anti-cancer by blocking IL-17 can prevent the development of AS characteristics in rats that spontaneously develop arthritis (13).

The values of IL-17 increase especially in patients with long-term disease.

In addition a recent study has given reason for the role of IL-17 in epidermal hyperplasia and bone destruction related with PsA (7). The authors proposed that the effect of IL-17A in inflamma-

tory arthritis is to make pre-osteoclasts cells hypersensitive to the RANKL signal and to increase RANKL serum. In the study, bone and joint destruction in the IL-17A gene transfer coincided with a skin pathology. Therefore, it is possible that IL-17A also induces the expansion of a second myeloid cell subset, associated with cutaneous pathology including epidermal hyperplasia and parakeratosis (4, 7, 8).

Furthermore, a recent work studied the pathophysiological role of IL-27 and VEGF in AS identifying the correlation with the activity of the disease (14). The authors detected that IL-27 concentration had increased in AS patients related with disease activity as indicated by BASDAI. They propose that in patients with peripheral arthritis, IL-27 acts by interacting with VEGF (14).

The cytokines produced during enthesitis and synovitis are also important in the contemporaneous presence of bone erosions and bone proliferation, typical of SpA. The disease involves bone reabsorption as well as bone formation (16). TNF-α induces osteoclast differentiation and suppresses osteoblast differentiation and new bone formation. This mechanism explains the increase of bone erosion but it does not clarify the bone formation (17, 18). Therefore, the new bone formation can be explained by the presence of other cytokines. Current therapy, which adequately controls inflammation in PsA and delays the evolution of bone erosion, does not block the new bone formation. This indicates that the mechanisms that connect inflammation to new bone formation are different from those linking inflammation with bone erosion. Sherlock *et al.* suggest that IL-22 produces T-cells important in the process of responses to local bone in SpA (16, 11).

However, the molecular mechanism, the new bone formation and pathological joint remodelling remain unclear (19-23). Other studies have described different pathways for the formation of new bone through specific proteins and mediators. De Bari *et al.* suggest that the shape and localisation of bony protrusions in the spine, in peripheral joints and extra-articular sites have a close connection with enthesis (24). Nevertheless, it has not been demonstrated that enthesis cells proliferate and differentiate into bone and cartilage enthesitis. Progenitor cells in periosteum and synovium can be subjected to differentiation. In particular, periosteal cells have a strong chondrogenic and osteogenic differentiation potential (25). As suggested by Marinova *et al.*, migration of bone marrow progenitor cells through small channels between the enthesis, synovium, and the underlying bone marrow may become an important contributor to the beginning and the progression of ankylosis (26, 27).

Three new differentiation and bone-forming processes have been suggested (28, 29). During the process of enchondral bone formation, the intermediate formation of a cartilage template forms new bone. In the cartilage the chondrocytes differentiate, attract osteoblast precursors cells, and are gradually substituted by bone (27-32). It is possible to find endochondral bone formation when a large amount of bone is being newly formed, for example in fracture healing. Direct or membranous bone formation is largely based on the positioning of bone carried out by osteoblasts (31-35). A third mechanism happens with the presence of cartilage metaplasia with calcification of the extracellular matrix surrounding chondrocytes (33). Additional are warranted to understand the connection between cytokines and anabolic factors and the reason why bone formation begins early in patients with PsA but is rarely present in patients with rheumatoid arthritis (RA).

Muscoloskeletal manifestations

Axial manifestations

Inflammatory back pain is a feature of axSpA. The rising manifestation of back pain for at least 3 months, associated with morning stiffness that improves with exercise in an individual aged 40–45 years or less, represents the ground for subsequent criteria for axSpA including the 2009 ASAS criteria (36). Depending on the definition used, about 25% to 75% of patients with PsA have axial involvement and experience inflammatory back pain and stiffness, together with spinal involvement on imaging (sacroiliitis, spinal ossifications) (36-38). Higher severity of back pain has been shown to be associated with higher levels of disease activity in patients with SpA (39). Skeletal damage is a consequence of bone destruction and unusual bone formation, which may occur simultaneously or in alternation. The formation and growth of syndesmophytes involve osteoproliferation, which contributes most to the structural damage typical of this disease (35). Syndesmophytes progression is highly variable in patients with axSpA, but in particularly severe cases it can lead to the complete fusion of the axial skeleton and even of peripheral joints.

A recent study showed that the most important predictors of progression of syndesmophytes that have been identified are the presence of existing syndesmophytes at onset, male gender and elevated serum levels of C-reactive protein. A strong habit of cigarette smoking has also been reported (40). The presence of erosions or sclerosis also increases the probability of a new syndesmophyte in that particular site two years later. In particular, sclerosis has been more strongly associated with the possibility of a new syndesmophyte than erosions. On the contrary, studies of serum proteins have not confirmed the identification of prognostic biomarkers yet. Although interesting studies are suggestive, no specific medication has been demonstrated to slow the growth of syndesmophytes (40). There is still a lot to learn about the factors underlying this process and additional investigation in this field is needed.

Peripheral manifestations

Enthesitis is often the first clinical manifestation of active SpA disease. Enthesitis is considered a pathological feature of the SpA group of conditions, including PsA. It is usually described as an inflammation of the insertion of tendons, ligaments and capsules into the bone (41, 42). The prevalence of clinically-detected enthesitis appears to be between 30% and 50% in patients with PsA and SpA (43).

Recent studies regarding the function, anatomy and pathophysiology of enthesis have clarified the understanding of the involvement of this anatomical

structure in the course of such diseases (44-45). It has also given confirmation of the initial observations regarding the importance of enthesitis to the pathogenesis and clinical manifestations of SpA and PsA (44). The reason because patients with PsA or SpA are likely to develop enthesitis is not fully clear. It depends on a multi-step process that consists of the beginning and the increase of the inflammation followed by local tissue responses leading to new bone formation. The process of enthesitis is marked by mechanical stress, innate immune activation and mesenchymal tissue modelling and remodelling. Distinct molecules and cells guide this process (44, 45).

The ASAS and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have recommended enthesitis as one of the best indicators for assessing disease activity and response in both axial and peripheral SpA and PsA (46-48).

The enthesis concept has been elaborated at length and fits well with many other concepts that are applied to SpA. Nevertheless, imaging and pathology studies have also demonstrated that not only enthesitis contributes to the signs and symptoms of the disease but also synovitis, arthritis and dactylitis (49-51). Dactylitis is defined by Rothschild as the "uniform swelling such that the soft tissues between the metacarpophalangeal and proximal interphalangeal, proximal and distal interphalangeal, and/or distal interphalangeal joint and digital tuft are diffusely swollen to the extent that the actual joint swelling can no longer be independently recognised" (52). It is a clinical result that is traditionally related to the diagnosis of PsA with peripheral manifestations but recent studies have shown that the presence of dactylitis is not exclusive in patients with PsA or peripheral disease (52, 53) but it is instead also a frequent manifestation in patients with early SpA even at its early stages (54). Dactylitis has been included as one of the typical hallmarks of the classification criteria for both axial and peripheral ASAS SpA (55).

Synovitis describes an intra-articular process where inflammation of synovial membrane is recurrent. Swelling, in addition to tenderness, is an important discriminator between inflammation and pain (44).

Some studies suggest that the pathogenetic basis of joint inflammation in SpA is based on the close anatomical relationship between entheses, affected by mechanical stress, and the synovium, affected by numerous immune mediators. It has been proposed to consider the functional unit formed by the synovium and enthesis as a single functional synovio-entheseal complex. It gives a physiopathological explanation and highlights the role of mechanical stress on specific tissues (56).

Extra-articular manifestations

Extra-articular manifestations such as anterior uveitis, psoriasis (Pso) and inflammatory bowel disease (IBD) are also typical for SpA.

A systematic literature review concludes that the mean prevalence of uveitis in SpA is 32.7%. It varies according to the type of SpA: 33% in AS and 25% in PsA (57).

Moreover the uveitis associated with AS affects male slightly more than females. On the contrary uveitis associated with inflammatory bowel disease affect women more frequently (58).

Uveitis associated with AS is often unilateral, recurrent and characterised by a rapid onset and anterior inflammation (59). On the other hand, uveitis associated with PsA and chronic intestinal diseases is a bilateral disease with an insidious onset and sometimes is posterior (62). Uveitis can also be an early extra-early-articular manifestation in a patient with SpA not yet diagnosed (60). It is therefore very important to know the association between uveitis and SpA for an early diagnosis and an early management of this disease to prevent potential disabilities

Pso occurs in more than 10% of patients with AS.

According to recent studies, there is a clear correlation between epithelial barrier inflammation and SpA, caused by shared genetic and environmental risk factors. At this point, speculating that epithelial barrier inflammation leads to arthritis through the transmission of immune factors or cells is tempting. Inflammatory bowel disease occurs in 5% to 10% of patients with AS, where Crohn's disease is more frequent than ulcerative colitis (61).

Comorbidities

SpA tends to associate with the development of some comorbidities, in particular with metabolic syndrome, osteoporosis, mood disorders and malignancy.

Metabolic syndrome

Metabolic syndrome is a cluster of classic cardiovascular (CV) risk factors including central obesity, dyslipidaemia, glucose intolerance, and hypertension, and it is identified as a strong predictor of CV disease, stroke, and type 2 diabetes mellitus (62). Its prevalence is high: 20–30% of the general population (63). A recent review of the literature concluded that prevalence increases in women older than 50 years. It is explained by genetic pathways and biological mechanisms such as hyperandrogenism, insulin resistance and the associated increase in abdominal obesity and HLD- cholesterol reduction that develop after the menopause (62). Metabolic syndrome is characterised by a low-grade chronic inflammatory state and by white adipose tissue. It regulates inflammation by secreting numerous pro- and anti-inflammatory proteins, called adipokines. Recent studies have described the association between metabolic syndrome and spondyloarthritis, specially with PsA (62, 64, 65). In particular, the association between axial SpA and PsA and the increased cardiovascular mortality has been reported.

Bakland *et al*. report a higher mortality rate in terms of standardised mortality ratio (SMR) ranging from 1.32 to 2.62 in axSpA compared to the general population, with cardiovascular disease as the main cause in most of the studies. The authors demonstrate that mortality ratio is more related to infrequent use of NSAID rather than a continuous one (66).

The presence of inflammation and the expression of pro-inflammatory cytokines are crucial in every phase of atherosclerotic process that could be enhanced in AS patients. This promotes

not only the development of arterial plaque but also its rapture (67). Recent meta-analysis highlighted that also patients with Pso have a 40% increased risk of developing cardiovascular diseases (68). An important recent study reported that the prevalence in RA, Pso and PsA cohorts for hypertension was 18.6%, 16.6%, 19.9%, respectively; in diabetes mellitus 6.2%, 6.3% and 7.8%; in hyperlipidaemia 9.9%, 10.4% and 11.6%; and in obesity 4.4%, 3.8% and 6.0% (69). The increased cardiovascular morbidity in psoriatic disease may be also partially associated with the high prevalence of metabolic abnormalities related with obesity, such as impaired glucose tolerance and atherogenic lipid profile, together with an unhealthy lifestyle (*e.g.* smoking, physical inactivity) that are frequent in these patients (70).

An important role in the pathogenesis of metabolic syndrome is played by white adipose tissue, which represents an endocrine organ able to produce many pro and anti-inflammatory molecules, regulating both inflammation and metabolic state (71). The prevalence of metabolic syndrome in PsA is 38% (72). A continuous production of some important cytokines and adipocytokines such as TNF, IL6, IL-1 β, leptin and adiponectin may be a result of excessive presence of white adipose tissue. The function of Th-17 derived cytokines in the pathogenesis of obesity and related inflammatory disease is also important. These molecules may cause the development of a pro-inflammatory state and may promote a subclinical inflammation at the level of vessel intima. This could result in atherosclerotic processes (73).

According to recent studies, the prevalence of diabetes seems higher in AS and PsA patients compared to the general population (74, 75). In particular tender joint count and ESR can predict the rising of diabetes.

Osteoporosis

Osteoporosis is a systemic skeletal disease associated with diminished bone mass, compromised bone strength and microarchitectural deterioration of bone tissue with a higher risk of fragility fractures (76). Osteoporosis of the spine and peripheral bones is common in SpA. The combination of spinal rigidity from the formation of syndesmophytes and osteoporosis in trabecular bone contributes to the risk of spinal fracture. This is as high as 10% in these patients and is connected with a high possibility of severe spinal cord injury (77). Bone mineral density (BMD), measured by DXA despite the presence of osteoporosis, may be increased by abnormal calcification of spinal ligaments, new bone formation in the spine and peripheral joints.

In axSpA, BMD may not be a sensitive marker for diagnosis osteoporosis. Bone loss connected with inflammation, limited physical activity, damaged kidneys, which may lead to secondary hyperparathyroidism, may all contribute towards a low BMD in axial SA. The prevalence of low BMD in axSpA has been found to vary between 11.7% and 34.4%, with the prevalence of fragility fractures ranging between 11% and 24.6%. (78). Risk factors such as age, use of steroids, low serum levels of 25OH vitamin D and smoking have been highlighted in AxSpA. Other risk factors like smoking, alcohol, familiarity with fracture and diet require to be investigated further. An early evaluation of risk factor is important to prevent fracture and possible future disability. Although inflammation of the axial skeleton frequently ends with the formation of bony spurs, osteopenia is detected in over 54% of AS patients.

It has been recently demonstrated that a higher bone loss caused by bone turnover, affects more the disease duration in correlation to the HLA-B27 gene than osteoblastic bone formation. In the study, an increased osteoclast-caused activity was highlighted. Additionally, the extracellular matrix of the bones lost some of its resistance to elastic and plastic deformation. Furthermore, the data indicate that IBD only plays a minor role in driving bone loss (79).

Mood disorders

As Shen *et al.* showed, AS patients seemed to have a higher risk of developing depressive disorders, anxiety disorders and sleep disorders due to sleep quality and disease activity (80). Lewinson *et al.* confirmed the occurrence of psychiatric disorders in AS patients. Moreover, having a major depressive disorder has been demonstrated to be a significant risk factor for the development of PsA (81).

A recent literature review also emphasises the risk of suicidal ideation and behaviour, particularly in patients with PsA (82). The symptoms associated with psoriasis such as pain, itching, scaling can limit the social life of patients. Arthritis can also create disability, affecting the ability to socialise.

The presence of functional disability, reduced mobility, pain, fatigue and, generally speaking, reduced quality of life, plays an important role on the development of mood disorders. Depression, anxiety and sleep disorders are found at all stages of the illness so the disease activity does not correlate with mood disorders (83).

Furthermore, Raison *et al.* have concluded that inflammation connected with chronic inflammatory conditions has an important role in the pathophysiology of depression. High levels of C-reactive protein were also linked to the presence of these disorders in SpA (84).

Also pro-inflammatory cytokines such as IL 1 and IL 6 are elevated both in psoriasis and in depression, indicating that high levels of cytokines in the central nervous system can cause physiological and biochemical changes that can contribute to the development of depression (85).

However, the exact molecular mechanisms remain unexplained. Further studies will be needed to understand the effect of systemic inflammation on mood disorders.

Fibromyalgia

Fibromyalgia (FM) is the most frequent diagnosis in patients that suffer from chronic diffuse pain with fatigue. It can occur alone or in association with chronic inflammatory diseases (86). The prevalence of FM ranges from 2% to 8% in the general population and it can get to over 50% in patients with other rheumatic and musculoskeletal diseases (87). In particular the presence

of FM has been reported in 4% to 25% of patients with axSpA and 9% to 17% in PsA (66). Sometimes the differential diagnosis between tender points and enthesitis can be difficult. In most cases of enthesitis there are no visible signs of clinical inflammation or increased acute phase reactants (88). Moreover, many entheses are difficult to access clinically, because they are located deep inside the human body. Occasionally, there is also an overlap with FM tender points (89).

Finally, clinically detected enthesitis in SpA may be extremely complex to tell apart from tender points in FM. This means that disease activity measures that include subjective elements, such as pain and patient global reports may be increased, even when more objective measures, such as swollen joint count or CRP suggest remission or low disease activity (84). This should be considered in the treatment algorithm so to avoid unnecessary and excessive treatment (90).

In this context imaging, especially ultrasound (US), can play an important role in detecting enthesitis. Recently, the EULAR recommendations for the use of imaging in the diagnosis and management of SpA advise the use of MRI and US for diagnosis, activity monitoring and structural change evaluation in peripheral SpA (91). It has been demonstrated that US has a good accuracy, reliability and sensitivity to change in the assessment of structures involved in PsA, such as entheses, but also tendons, synovium and bones (92). A recent review of the literature highlighted the role of ultrasound, in particular the Doppler signal in entheses rather than grey-scale changes, as a specific element in PsA (93). Therefore, the integration of the US with the clinical examination can be an important support in the diagnostic process.

Malignancy

In the last years, researchers have investigated the association that exists between malignancy and autoimmune diseases. Numerous studies have reported a higher risk for cancer in patients with autoimmune diseases (94). It seems that chronic inflammation could increase the risk of malignancy, because the occurrence of bone cancer, colon cancer, prostate cancer was significantly higher in patients with AS (66). In particular, female patients with SA were found more likely to develop colon cancer (95).

A significantly higher risk was observed for AS patients aged between 50 and 64 years old (89) with a 14% increase in the overall risk for tumour of the digestive system, multiple myelomas and lymphomas (96). Another recent study concluded that the risk for lung or head and neck cancer among patients with AS was significantly higher. On the contrary, risks for liver, bladder, and uterus cancers were only marginally important (97). These various effects on cancer risk may be caused by chronic inflammation (98). However, the current literature does not prove that an association of anti-TNF and IL-17 agents with malignancy in patients with SpA exists (99). What has not been shown is an increase in the risk of tumours for the inhibitors of IL12/23 (100). Additionally, patients with a primary malignancy may develop autoimmune-like disease. The literature highlights an association also between cancer and many other inflammatory diseases, such as inflammatory bowel disease, RA, systemic lupus erythematosus, multiple sclerosis and others. These data call for attention towards patients with rheumatic diseases for early identification of cancer in clinical practice and to improve the quality of care of these patients.

Conclusions

SpA constitutes a group of complex diseases. Enthesitis is one of its feature elements, but also many musculoskeletal and extra-articular manifestations play an important role. Numerous comorbidities can also be associated with this disease.

Recent studies have illustrated interesting theories on the physiopathological mechanisms, although at the moment these have yet to be fully explained.

More studies and investigations aimed at understanding these complex pathologies with the ultimate goal of a more prompt and effective care of these patients are warranted.

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