

Pathophysiology of bone and cardiac involvement in spondyloarthropathies: The indispensable value of magnetic resonance imaging

Mavrogeni SI^{1,*}, Nikas I², Bonou M³, Kitas GD⁴

¹Onassis Cardiac Surgery Center, Athens, Greece

²Bioiatriki MRI Unit, Athens, Greece

³Cardiology Dpt, Laikon Hospital, Athens, Greece

⁴Arthritis Research UK Epidemiology Unit, Manchester University, Manchester, UK

Abstract

Spondyloarthropathies (SpA) include a group of inflammatory arthritides encompassing ankylosing spondylitis (AS), reactive arthritis, arthritis/spondylitis associated with psoriasis (PsA) and arthritis/spondylitis associated with inflammatory bowel diseases (IBD). In SpA, inflammation can act either by promoting atherosclerosis or by increasing the effect of conventional CV risk factors. The incidence of cardiovascular (CV) disease in AS is 10-30% and includes aortic valve regurgitation, aortitis, atrioventricular (AV) and/or bundle branch block. In PsA and IBD, there is increased risk of CV events, because high levels of cytokines promote atherosclerosis. Furthermore, the persistence of systemic inflammation promotes the development of myocardial inflammation

Magnetic Resonance Imaging (MRI) can identify inflammation in the early stage of SpA, which usually occurs years before the development of structural lesions. Bone marrow edema (BME) has been detected not only at sacroiliac joints, but also at the spine, and it is considered as the hallmark of inflammation. Cardiovascular magnetic resonance (CMR) allows function and tissue characterization and detects subclinical cardiac lesions, including myocardial oedema, myocarditis, replacement and diffuse myocardial fibrosis, despite the presence of well controlled musculoskeletal disease.

Considering that bone radiographic, cardiac echocardiographic findings and serum biomarkers are late markers of bone and heart involvement, MRI/CMR can play an indispensable role for early diagnosis/follow up of bone/heart disease in SpA.

Introduction

The term of spondyloarthropathies (SpA) describes a group of inflammatory arthritides encompassing ankylosing spondylitis (AS), reactive arthritis, arthritis/ spondylitis associated with psoriasis (PsA) and arthritis/spondylitis associated with inflammatory bowel diseases (IBD). The human leukocyte antigen (HLA)-B27 positivity, peripheral joint involvement mainly of the lower extremities, sacroiliitis, spondylitis, enthesitis, dactylitis, uveitis, enteric mucosal lesions and skin lesions are the classic manifestations of these diseases [1-3].

The recently developed Assessment of SpondyloArthritis International Society (ASAS) classification criteria proposed the classification of SpA according to the main clinical manifestations including either predominantly axial or predominantly peripheral presentation, with or without coexisting psoriasis, IBD or preceding infection [4-8]. Inflammatory back pain (IBP), the leading symptom of the SpA, is due to inflammation of sacroiliac joints, spine and spinal entheses. However, the sensitivity and specificity of IBP for diagnosis of axial SpA is only 80% [6,7]. HLA B-27 positivity is an important index for the early diagnosis of SpA. Five to 10% of the population is HLA B-27 positive. However, in patients with AS and other SpA the positivity of HLA B-27 reaches 70% - 95% and 70%, respectively [8].

Type of spondyloarthropathies

Ankylosing spondylitis

Ankylosing spondylitis (AS) is the commonest expression of SpA. It is 2-3 times more common in men than women. IBP in a young patient is the most frequent symptom, but peripheral arthritis and/or enthesopathy may be found in some patients. Uveitis, positive family history for AS, impaired spinal mobility or chest expansion, all supports the diagnosis of AS [1].

Axial involvement is one of the disease characteristics and 90% of patients have radiographic sacroiliitis during the course of the disease. Currently, a patient can be classified as having definite AS, if at least one clinical criterion (IBP, limitation of lumbar spine or limitation of chest expansion) plus a radiologic criterion (bilaterally grade 2 or unilateral grade 3-4 sacroiliitis) are fulfilled [9].

***Correspondence to:** Prof. Dr. Sophie Mavrogeni, MD, PhD, FESC, Onassis Cardiac Surgery Center, Athens, Greece, E-mail: sophie.mavrogeni@gmail.com

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Axial spondyloarthritis

Unfortunately, sacroiliitis appears on plain radiographs years after the onset of IBP. Therefore, in 2009, ASAS developed two sets of criteria for classification of axial SpA that include patients without definite radiographic sacroiliitis [10]. The new criteria include a 'clinical arm' and an 'imaging arm'. The positivity of both "arms" had 82.9% sensitivity and 84.4% specificity, while the positivity of the 'imaging arm' alone had a sensitivity of 66.2% and specificity of 97.3%. ASAS criteria are simple and easily applicable in every day clinical practice [11-15].

Peripheral spondyloarthritis

After the development of ASAS criteria for axial SpA, ASAS experts developed criteria for SpA patients with predominant peripheral symptoms. The sensitivity of the criteria was 77.8% and the specificity was 82.2%. The new ASAS classification criteria for peripheral arthritis perform better than the previously used criteria [10].

Psoriatic arthritis

Psoriasis is a common disease affecting nearly 1% -2% of the population. In some forms of SpA, concurrent psoriasis may also occur. Psoriasis may precede, occur in parallel, or appear years after the onset of arthritis. In latter cases, patients may be misdiagnosed as having other types of arthritis, such as seronegative RA or reactive arthritis; however, positive family history for psoriasis is of great help in these cases. Patients with arthritis should be also evaluated for potentially "hidden" psoriatic lesions, located under the breasts, around the umbilicus or anus, over the hairline, nasal cleft or nails [11].

Patients with PsA usually present inflammatory axial involvement similar to AS. However, there are several differences compared to AS [11] including the presence of asymmetrical sacroiliitis, non-marginal syndesmophytes, asymmetrical syndesmophytes and more frequent involvement of the cervical spine [11].

Arthritis in Inflammatory bowel disease

Two types of joint involvement occur in patients with IBD including a) arthritis (inflammation) and b) arthralgia (pain without inflammation). Arthralgia is more common in IBD, occurring in 40-50% of patients, a rate similar to that of the general population. Arthritis occurs in 15-20% of Crohn's disease (CD) patients and approximately 10% of ulcerative colitis (UC) [12].

Approximately 60-70% of arthritis in IBD has the characteristics of peripheral oligo-arthritis with <5 joints affected. The most affected joints are the knees, ankles, wrists, elbows and hips. A smaller proportion of IBD patients have symmetrical polyarthritis of the small joints of the hands. Finally, 1-6% of all IBD patients develop AS affecting the sacroiliac joints and the spine. While large joint arthritis is almost always associated with active IBD, AS and small joint polyarthritis appear independently of the patient's IBD [12].

Cardiovascular involvement in SpA

Ankylosing spondylitis

The incidence of cardiovascular (CV) involvement in AS ranges between 10% to 30% [13] and may be presented as aortic valve regurgitation, aortitis of the ascending aorta, atrioventricular (AV) and/or bundle branch block. The most frequently observed complications are conduction defects and aortic regurgitation. Mitral regurgitation in AS is rare but may lead to heart failure (HF) [14-17]. CVD is more frequent in patients with long-term AS and peripheral joint involvement [18].

The incidence of aortic dissection has been reported about 2.9 in 100,000 [19] and represents the most fatal complication of the disease [20]. The most frequently observed symptom in AS patients is chest pain; however, it may have atypical findings including lack of pain or development of cardiac, neurological symptoms or evidence of ischemic extremities [21,22]. Aortic dissection is generally observed between the ages of 50-70 years and the ratio of men to women is 2:1 [21].

The main sources of stroke in AS are the lesions of the proximal aorta, but paraplegia may develop, due to distal lesions involving the spinal arteries. Although stroke and paraplegia develop rarely, their incidence in cases of aortic dissection is ranged from 2% to 8% [23].

Psoriatic Arthritis (PsA)

PsA has an increase in risk of clinical and subclinical CVD, mainly due to accelerating atherosclerosis. Both conventional and nonconventional CV risk factors contribute to increase atherosclerosis with consequent increase of CV risk. Although conventional risk factors occur more frequently in patients with PsA, they can only partially explain the excess of CV risk. It seems that inflammation is an important precipitating factor for the increased CV risk in PsA. Inflammation can act either by directly promoting the development of atherosclerosis or by increasing the effect of established conventional CV risk factors [24]. Furthermore, systemic inflammation can also precipitate myocardial inflammation [24].

Inflammatory bowel disease

Patients with IBD are at increased risk of CV events. High levels of cytokines, C-reactive protein (CRP) and homocysteine in IBD may contribute to endothelial dysfunction finally leading to atherosclerosis. Although IBD patients do not present the typical risk factors for CVD, changes in lipid profiles similar to those seen in patients with CV events have been reported. Furthermore, increased levels of coagulation factors, frequently occurring in IBD, may predispose to arterial thromboembolic events. Finally, the gut itself may have an impact on atherogenesis through its microbiota. Microbial products are released from the inflamed intestinal mucosa into the circulation through a leaky barrier. As a consequence, the increase of proinflammatory cytokines contributes to endothelial damage and CV events [25].

The link between bone and cardiac inflammation

There is a link between bone inflammation in SpA and CVD development which was usually attributed to coronary artery disease (CAD). However, the commonest CVD expression in SpA is heart failure (HF), which may start at diagnosis and increases proportionally to duration and severity of the systemic inflammation. However, it should be noted that HF in SpA is not the result of epicardial coronary artery disease, but is related to myocardial inflammation, coronary microvascular dysfunction and fibrosis, all of them leading to heart failure with preserved ejection fraction (HFpEF) [26].

Pro-inflammatory mediating factors that are characteristic of systemic inflammation such as leptin, aldosterone and neprilysin can cause expansion and biological transformation of epicardial adipose tissue (EAT) leading to coronary microvascular injury and myocardial fibrosis [27]. In patients with expanded EAT, the release of leptin and aldosterone promote myocardial inflammation, microcirculatory dysfunction and fibrosis [27]. These effects are opposed to the anti-inflammatory and anti-fibrotic actions of endogenous natriuretic peptides [28] and lead to impairment in the distensibility of the left ventricle (LV). Therefore, blood volume is regulated only due

to an increase in cardiac filling pressures. This finally leads to exertional dyspnoea and HF. EAT volume is increased in SpA and 30–50% of affected patients have subclinical cardiac inflammation, microcirculatory dysfunction and fibrosis finally leading to HFpEF.

SpA patients are characterized by increased levels of aldosterone in blood and inflamed tissues [29] and therefore, spironolactone, an aldosterone antagonist, has been proposed as a treatment for these arthritides. At the same time, the increased levels of leptin in blood and synovial fluid, found in SpA, are associated with the extent of joint/bone involvement and linked with patient-reported symptoms and disease activity [30]. Interestingly, high levels of leptin may identify SpA patients, who respond poorly to anti-inflammatory treatment [31].

The currently used anti-inflammatory agents in the treatment of SpA have the potential to reduce the risk of cardiac involvement and HFpEF [32]. In addition, it is possible that drugs modulating the leptin-aldosterone-nephrilysin axis could modify the CV consequences of systemic inflammation and change the clinical course of HFpEF in these patients [33].

Imaging bone and heart involvement in SpA

The indispensable role of magnetic resonance imaging

The pathophysiologic mechanisms, already discussed, make clear the correlation between the systemic inflammation and the development of CVD and emphasize the need for a concurrent assessment of both bone and cardiac inflammation. In this context, the role of a sensitive and reproducible imaging modality that can identify early the presence of inflammation is of great value for both bones and heart. The role of various modalities in the early inflammation identification in bones and heart is described below

Role of imaging for bone/joint assessment in SpA

The imaging of the sacroiliac joints and the spine plays an

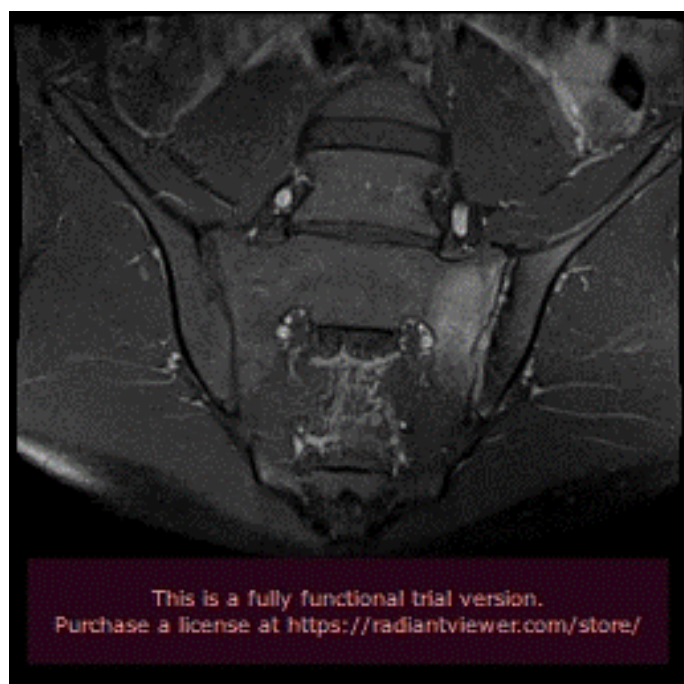


Figure 1. Semicoronal STIR image shows bone marrow edema especially at the sacral side of the left sacroiliac joint and moderate synovium edema.

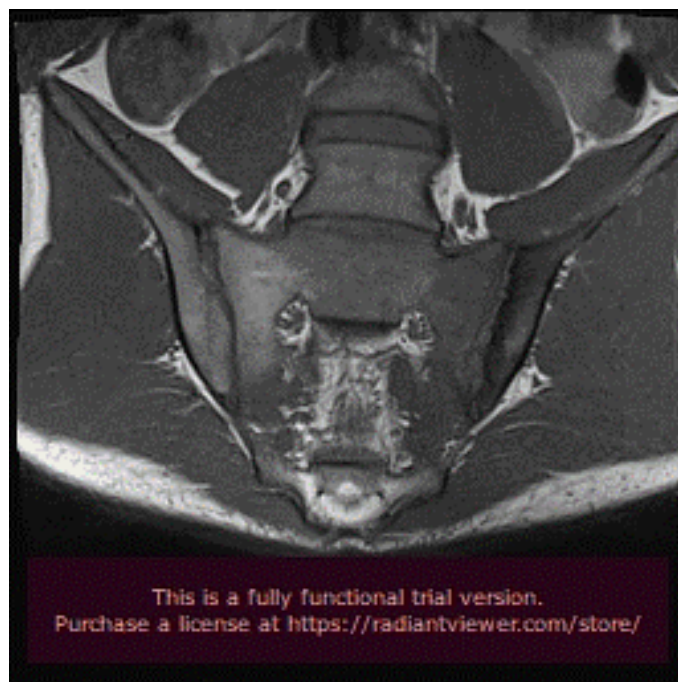


Figure 2. T1w image shows low signal abnormalities due to marrow edema and mild sclerosis of the iliac side endplate.

important role in the diagnosis and monitoring of SpA. Sacroiliitis on conventional radiography was used as an important criterion for AS diagnosis. Usually, bilateral grade ≥ 2 or unilateral grade ≥ 3 sacroiliitis are considered typical for the diagnosis of AS [13]. However, radiographic sacroiliitis reflects changes late in the course of the disease and only in a subgroup of SpA patients [12].

The introduction of magnetic resonance imaging (MRI) in the clinical practice has changed dramatically the diagnostic algorithm of SpA, because MRI-detected sacroiliitis has been included in the new Assessment of SpondyloArthritis Society (ASAS) classification criteria for axial SpA, as a basic diagnostic tool [34]. Prior to this innovation, radiological sacroiliitis was diagnosed on the basis of x-rays, where changes can be detected only at advanced stages of the disease and therefore, they have low specificity for patients in early stages of the disease. In contrast, MRI can identify inflammation in the early stage of SpA, which usually occurs years before the development of structural lesions. Bone marrow edema (BME) has been detected not only at sacroiliac joints in axial SpA, but also at the spine, and it is considered as the hallmark of inflammation (Figure 1 and Figure 2). Among inflammatory lesions that can be detected on MRI at the sacroiliac joints, only BME has been considered as a reliable index in the identification of active sacroiliitis [35]. This finding is thought to reflect the presence of osteitis and correlates with histologically documented inflammation. Bollow et al. [36] demonstrated an inflammatory infiltrate of T-cells, macrophages and scarce B-cells in biopsy of patients with MRI-detected sacroiliitis. Moreover, they found a higher number of inflammatory cells in patients with active sacroiliitis on MRI, but not in patients with chronic sacroiliitis. Recent studies support that not only the presence, but also the severity of BME is important for the disease diagnosis. In a prospective study of 40 patients with IBP, the presence of severe sacroiliitis in association with HLA-B27 positivity was highly predictive of a diagnosis of AS at 8 years, with a positive likelihood ratio of 8.0. In contrast, patients with mild or no BME had a low likelihood to develop AS [37]. In another study comparing patients with IBP with

patients with mechanical back pain or healthy volunteers, BME of the sacroiliac joints was found also in the control group, although it was less frequent compared to patients with IBP. The very early IBP of SpA can be differentiated from non-SpA, based on BME severity [38].

MRI can identify active inflammation at sacroiliac joints and spine in established or early axial disease, independently of disease stage [10]. ASAS classification criteria for axial SpA have 2 arms: an imaging and a clinical arm. The imaging arm includes either sacroiliitis on conventional radiography or on MRI, which is of indispensable value for the recognition of pre-radiographic changes in early SpA [4]. Regarding spondylitis, which may also occur before sacroiliitis, the diagnosis of a “positive MRI” for spinal inflammation is also needed [39]. However, there are insufficient data regarding the use of spinal MRI and the specificity of spinal findings in the axial SpA diagnosis [40].

Active inflammatory lesions (bone marrow edema, osteitis, synovitis, enthesitis, capsulitis) and structural damage (sclerosis, erosions, fat deposition, ankylosis) can be detected by MRI. ASAS/OMERACT imaging group defined that a minimum amount of BME in one lesion of at least two adjacent slices or more than one lesion at least in one slice is required for the definitive diagnosis of sacroiliitis [41].

MRI can also assess the evolution of spinal damage of AS. Usually, it begins with bone inflammation that may be visible as osteitis, typically seen on a short tau inversion recovery (STIR/T2) image of the MRI [42,43]. To repair the tissue, subchondral bone marrow is replaced with fatty metaplasia, which presents as a fatty lesion on a T1 weighted MRI scan [42,43]. Inflammation or intermediate stage fatty lesions may play an important role in the development of new bone formation (structural damage), emphasizing the need for early deterioration of inflammation to reduce risk of further bone damage [43]. Almost 60% to 70% of AS patients develop irreversible structural changes leading in spinal fusion and reduced spinal mobility [43,44]. Although AS patients usually present reduced physical/spinal function, due to structural lesions and inflammation, in patients with non-radiologic positive SpA (nr-axSpA), this functional disability is typically due to inflammation alone [44]. Risk factors for progression of spinal disease in AS patients include male sex, presence of syndesmophytes at baseline, elevation of CRP and smoking (in men) [45].

Recently, several studies have examined the MRI characteristics of new bone formation in axial skeleton in patients with SpA and assessed findings that showed potential markers of disease progression [46-52]. The intra-articular high signal intensity on T1-weighted MR images known as “Backfill” with high signal intensity similar to adipose tissue on T1-weighted MR images in the sacroiliac joint space was considered as a metaplastic tissue refilling of the eroded subchondral bone [46,50,51]. There is no consensus about the clinical value of this finding, because until now there is no histopathological evaluation of this lesion [50]. However, this intra-articular high signal intensity on T1-weighted MRI images of the sacroiliac joints has been documented in 38–63% of SpA patients ≤45 years old and had a high diagnostic value for this disease [46,50]. There is also supported that this finding should be considered stronger than the classic ASAS criteria for SpA sacroiliitis, even if there is no concurrent BME [51].

Ankylosis of the sacroiliac joints is the typical finding of end-stage axial SpA. This may appear as low signal intensity obliteration of articular cortical margins, on most MRI sequences, but it may present high signal intensity on T1-weighted MR images, when the subarticular bone marrow crossing the sacroiliac joint has high-fat content [50,51].

The presence of discal high signal intensity on T1-weighted MR images, which has only been evaluated in a limited number of patients,

has high signal intensity similar to adipose tissue on T1-weighted images within the intervertebral disc and was considered as an early discal calcification [52-58]. In a recent study, it was considered as highly specific for SpA, although it needs further validation [52].

Syndesmophyte formation is defined as bony growth originating from the Sharpey fibers of the annulus fibrosus [52]. On sagittal spinal MRI, syndesmophytes will be observed as longitudinal bony outgrowths at the anterior and posterior corners of the vertebral bodies, oriented craniocaudally. The signal intensity on T1-weighted images is isointense or hyperintense to red bone marrow—in case of presence of fatty bone marrow [52]. However, non-bridging syndesmophytes in the absence of other findings of new bone formation were only seen in patients without SpA [21] and therefore, they should not be used for SpA diagnosis or follow up. Vertebral corner bridging also known as “bridging syndesmophytes” or “ankylosis within the annulus fibrosus” [52] is observed in the anterior or posterior corners of the vertebral bodies, at the Sharpey fibers of the annulus fibrosus of the intervertebral disc [52]. The signal intensity on T1-weighted images is isointense or hyperintense to red bone marrow, in case of fatty bone marrow [52]. In contrast to non-bridging syndesmophytes, this MRI feature is specific for SpA [52].

Transdiscal ankylosis, also known as “non-corner ankylosis” [52], is defined as bone fusion crossing the vertebral joint space through the expected location of the nucleus pulposus in the intervertebral disc, with obliteration of the cortical margins of the vertebral body [52]. Similar to syndesmophytes, the signal intensity on T1-weighted images is isointense or hyperintense to red bone marrow, in case of presence of fatty bone marrow [52]. This finding is specific for axial SpA [52] and is considered a marker of late disease, because axial SpA almost always starts in the sacroiliac joints, typically leaving the spine unaffected for long time. However, it may also be found in younger patients with more severe disease [52].

Role of imaging for cardiac assessment in SpA

The main imaging modalities used for evaluation of myocardial status in SpA include echocardiography and cardiovascular magnetic resonance (CMR). Subclinical cardiac dysfunction was identified in AS patients despite well controlled musculo-skeletal disease, using echocardiography [59]. Furthermore, aortic stiffness and left ventricular global longitudinal strain (LVGLS) were increased in AS patients [59]. In another echocardiographic study, early, subclinical myocardial dysfunction was observed in inflammatory joint disease (IJD) patients with preserved left-ventricular ejection fraction, but without traditional CV risk factors. In these patients, disease activity was the main predictor of myocardial strain impairment [60]. In another study, it was documented that AS patients had lower LVGLS compared with controls, independently of confounders. Furthermore, lower LVGLS was associated with larger aortic root diameter [61]. Finally, most asymptomatic SpA patients have concentric LV remodeling, which is closely associated with subclinical left ventricular systolic dysfunction (LVSD) [62]. Echocardiography, although it is an easy, low cost and widely available modality, it has the limitations of operator and acoustic window dependency and cannot perform cardiac tissue characterization [63].

In contrast to echocardiography, CMR is operator and acoustic window independent and can provide function and tissue characterization information noninvasively in the same examination [63]. A CMR study, including AS patients with abnormal findings on screening echocardiography, identified that aortic arch pulse wave velocity (PWV) was significantly higher in the AS group compared



Figure 3: STIR T2 image of the heart showing myocardial oedema in a patient with AS.

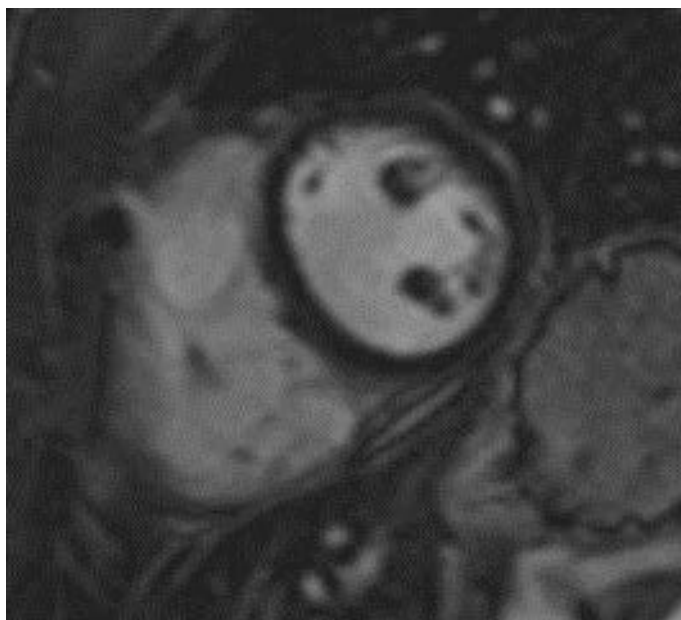


Figure 4: Inversion recovery image of the heart showing subepicardial LGE in the lateral wall in a patient with PsA.

with the controls [64]. Higher PWV in the aortic arch was associated with functional disability, the presence of non-ischemic hyperenhancement and reduced LV systolic function [64]. In another CMR study in AS patients, global LV dysfunction and focal areas of hyperenhancement was identified. Myocardial extracellular volume fraction (ECV) was associated with the degree of disease activity [65]. Furthermore, occult CMR lesions, including oedema, myocarditis (Figures 3 and Figure 4), diffuse subendocardial fibrosis and myocardial infarction are not unusual in treatment naïve SpA patients and may be reversed with appropriate treatment [66]. Recently, anti-TNF treatment, applied in SpA patients, reduced subclinical myocardial inflammation and improved CV function proving that CMR may have a place to assess CV disease progression and response to treatment [67].

MRI versus biomarkers in SpA

The evaluation of biomarkers in SpA is of particular interest, because the two most commonly used biomarkers, erythrocyte

sedimentation rate (ESR) and C-reactive protein (CRP), are of very low sensitivity and specificity. The second reason is the need for cost-effectiveness assessment after treatment of SpA patients with the very expensive tumor necrosis factor-alpha (TNF-alpha) blockers. In these cases, the clinicians need to be much more accurate in predicting disease progression, evaluating disease activity and monitoring therapeutic efficacy [68]. Furthermore, according to the results from the SpondyloArthritis Caught Early (SPACE) cohort the disease process in axial spondyloarthritis is not reflected by alterations in blood inflammatory indices such as CRP, ESR and Calprotectin. Additionally, serum levels of interleukin-27 (IL-27), human β -defensin-2 (hBD-2) and lipocalin-2 (LCN-2) were also not elevated. In contrast, the direct visualization of the inflammatory process might be a more successful approach to identify imaging biomarkers for axial SpA [69].

Regarding the cardiac evaluation, troponin and BNP are the most commonly used biomarkers. In the appropriate patient, an elevated troponin indicates heart damage and should prompt urgent inpatient investigations, while a normal troponin indicates low risk, but not absence of risk. Furthermore, troponins may be falsely elevated in certain situations and do not always indicate heart attack. These situations include myocarditis, Takotsubo syndrome, pulmonary embolism and trauma including also cardioversion or defibrillation [70]. Finally, the prevalence of an increased troponin T in biopsy-proven myocarditis, is only 35–45% [71].

More specifically in patients with axial SpA, both reduced longitudinal strain (LS) and elevated serum high-sensitivity troponin I (hsTnI) are promising independent predictors for CV events and those with $LS \geq -17.5\%$ and $hsTnI \geq 3.0$ pg/ml are at the highest risk of CV events [72].

It is impressive that although MRI has been used very early in the assessment of bone/joints, its application on cardiac evaluation of SpA patients has been only recently applied. There are many reasons for this including:

- 1) At the very first moment of its application MRI was considered as the ideal tool to assess bones and soft tissues. Therefore, it was introduced very early in the diagnostic algorithm of SpA [34]
- 2) Cardiovascular magnetic resonance (CMR) is a more overdemanding application that has become only recently available to cardiologists. Additionally, cardiologists are “obsessed” [63] with echocardiography, which is a modality unsuitable to detect myocardial inflammation, because it cannot perform tissue characterization.

Under these circumstances, only parameters available by echocardiography such as aortic dilatation or diastolic dysfunction were considered as serious cardiac complications in SpA. Furthermore, although HFpEF is the main cause of CV death in SpA, information regarding acute myocardial inflammation/fibrosis was completely ignored, due to the inability of echocardiography to detect these phenomena [63]. Finally, the knowledge that CV involvement may exist before or at diagnosis of various SpA [66], suggests that CMR should be considered in the diagnostic algorithm of CV assessment of SpA. At the moment published literature regarding CMR in SpA is poor. However, the need to assess myocardial inflammation/fibrosis as an effort to prevent the development of HFpEF in SpA patients should motivate further multicenter studies to establish the role of CMR in the SpA guidelines for CV evaluation.

Conclusions

Inflammation is the fundamental pathophysiologic background of bone/heart lesions in SpA patients. Since blood inflammatory indices are of limited value to assess bone/heart disease activity, there is a tremendous need for a targeted imaging approach. Bone MRI has been already included in the diagnostic algorithm of SpA, but the assessment of myocardial inflammation/fibrosis, using CMR, is still not included in the routine evaluation of SpA. However, the fact that HFpEF represents the main cause of CV mortality in SpA, suggests that a reconsideration of cardiac evaluation in SpA is needed.

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