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Axial spondyloarthritis—current aspects

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Abstract

Axial spondyloarthritis (axSpA) is a frequent inflammatory rheumatic disease mainly affecting the axial skeleton causing inflammatory back pain. If chronic inflammation persists new bone formation may occur possibly leading to irreversible spinal stiffness. The disease has a strong genetic background with HLA-B27 as the major factor. For diagnostic purposes, imaging is of critical importance—especially conventional radiography and magnetic resonance imaging (MRI). While the former has advantages in the detection of bony changes such as the syndesmophytes, MRI is used to detect axial inflammation but also erosions in the sacroiliac joint. Treatment follows the treat-to-target strategy starting with non-steroidal anti-inflammatory drugs (NSAIDs) in the first line, and later, if high disease activity persists, therapy with biologic disease modifying anti-rheumatic drugs (bDMARDs) is according to international recommendations indicated. For the treatment of axSpA, important targets such as tumor necrosis factor alpha (TNFα) and interleukin (IL)-17 have been identified, and several of their inhibitors (i) including some biosimilars for the former have been approved. Recently, also inhibition of Janus kinases was shown to be efficacious. There is evidence that long term inhibition of inflammation with TNFi can reduce bone formation.

Keywords

Ankylosing spondylitis, HLA-B27, TNFα, IL-17, Janus kinase

Introduction

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease that is clinically characterized by chronic back pain, mostly of the typical type, called inflammatory back pain (IBP). This condition is caused by inflammatory processes in the axial skeleton of varying intensity, including affection of the sacroiliac joints (SIJ), especially in early disease, and the spinal column (SC). These changes are initially caused by

inflammation and later on by new bone formation. These structural changes rather characteristically appear often in the form of syndesmophytes, erosions, and ankylosis in the axial skeleton.

In addition, there are various other disease manifestations and comorbidities belonging to the overall concept of spondyloarthritides (SpA) [1, 2] which include anterior uveitis (AU), psoriasis, and inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis [1, 2]. Common comorbidities are arterial hypertension, coronary heart disease, and osteoporosis [3]. An increased cardiovascular mortality in axSpA has been documented [4, 5].

The term axSpA has now replaced the term used for a long time, ankylosing spondylitis (AS) [6]. The term Morbus Bechterew, still used in German-speaking countries but not internationally, today mainly gives the name to the large German patient association DVMB.

This change to the term axSpA was necessary for two quite different reasons. On the one hand, the imaging procedure of magnetic resonance imaging (MRI) has revolutionized diagnostics in the area of axSpA, especially with regard to the SIJ and the SC. The main effect is that it has become possible to detect sacroiliitis much earlier [7]. On the other hand, it became apparent that biologic disease modifying anti-rheumatic drugs (bDMARDs) targeting tumor necrosis factor alpha (TNFα), developed in the 1990s and increasingly available since the early 2000s, are able to improve the symptoms of patients with axSpA, in some cases dramatically [8]. TNF inhibitors (TNFi) were the first bDMARDs, including infliximab, etanercept, adalimumab, golimumab, and certolizumab. Later, interleukin (IL)-17A antagonists such as secukinumab, ixekizumab, and bimekizumab (the latter also blocking IL-17F) were also found to be efficacious, and finally, the targeted synthetic (ts) DMARDs, all inhibitors of one or more Janus kinases (JAK), tofacitinib, upadacitinib, baricitinib and filgotinib (the latter 2 are not approved for axSpA), joined in. Thus, a broad range of potent anti-inflammatory agents is now available to treat patients with axSpA. In contrast, anti-IL-6 and anti-IL-23 agents failed. In this review, we discuss the clinically relevant aspects of classification, diagnosis, and treatment of axSpA.

Classification criteria for axSpA

The use of the term AS was very much based on the so-called modified New York criteria of 1984, which were published as diagnostic criteria but are de facto classification criteria [9]. In fact, there are no diagnostic criteria for AS or axSpA, i.e. diagnosis is an individual effort and achievement that should always be reasonably justified. Nevertheless, the classification criteria propagated by the Assessment of Spondyloarthritis International Society (ASAS) in 2009 [10], being developed for groups of patients for the reasons mentioned above, which have been used regularly in clinical studies already for a long time, have now already been available for 15 years [11]. It is common knowledge that classification criteria are in general only applied when the diagnosis has already been made [12]. However, it is possible to check whether the diagnosis in question corresponds to these classification criteria. When developing such criteria, the gold standard used is usually the expert opinion of the rheumatologists who know their patients but the sensitivity and specificity of the ASAS classification criteria were not higher than 84% [10]. This means that 17% of patients in the study who were considered by the rheumatologist to have axSpA were not detected by the criteria (false negative), while 16% of patients who were considered by the rheumatologist not to have axSpA but were identified as such by the criteria (false positive). For clinical practice, this means that matching the criteria significantly increases the chance that axSpA is present, but it certainly does not mean that axSpA is certainly present if the criteria are met, nor that axSpA is not present if the criteria are not met [12]. The criteria have recently been tested in the not-yet-published CLASSIC study (NCT03993847)—with the aim of increasing their specificity. The results are currently discussed within the expert organizations ASAS and Spondyloarthritis Research and Treatment Network (SPARTAN).

That the diagnosis of axSpA is not easy can be seen from the fact that on average it still takes more than 5 years after the onset of typical symptoms until the diagnosis is made these days [13]. At the same time, there is a relevant risk of overdiagnosis of axSpA in patients with mechanical and/or degenerative problems in the axial skeleton.

Basically, a distinction can be made between very early (symptom duration < 2 years), early (< 5 years), and diagnosis with already established disease (> 5 years). The ASAS group has recently proposed 2 years for the term early diagnosis of axSpA [14].

In the following, we will first deal with very early and early diagnosis (Table 1), and later with diagnosis of already established disease (Table 2).

Table 1. Possible building blocks for the diagnosis of axSpA (based on the ASAS classification criteria)—part 1: early diagnosis

Nr	Feature	Description/Definition	Decision
1	Back pain 1	Chronic ≥ 3 months in people < 45 years of age	Present yes/no
2	Back pain 2	Inflammatory = morning stiffness > 30 minutes, improvement with exercise, no improvement with rest, nocturnal awakening in the 2nd half of the night, insidious onset	At least 3 of those, better 4. Present yes/no
3	Imaging	MRI, X-ray, computed tomography of the sacroiliac joints and/or the spine	Positive findings regarding inflammation and/or structural changes Past or present yes/no
4	Lab test 1	HLA-B27	Present yes/no
5	Lab test 2	C-reactive protein	Elevated yes/no
6	Other musculoskeletal signs of SpA	Peripheral arthritis, enthesitis, dactylitis	Past or present yes/no
7	Extramusculoskeletal signs of SpA	Anterior uveitis, psoriasis, inflammatory bowel disease (Crohn's disease or ulcerative colitis)	Past or present yes/no
8	History	Positive family history of SpA	Present yes/no
9	Response to therapy	Good response to non-steroidal anti-inflammatory drugs (NSAIDs)	Past or present yes/no
10	Exclusion	Other important reasons for the presenting symptoms (see text: explanations of the individual building blocks for the diagnosis of axSpA)	Absence yes/no

axSpA: axial spondyloarthritis; ASAS: Assessment of SpondyloArthritis International Society; SpA: spondyloarthritides; Nr: number; MRI: magnetic resonance imaging. For more explanation see the text: explanations of the individual building blocks for the diagnosis of axSpA

Table 2. Possible building blocks for the diagnosis of axSpA—part 2: later diagnosis

Nr	Feature	Assessment	Decision
1	Limitation of spinal mobility	BASMI and thoracic excursion	Score > 3
2	Limitation of function	BASFI	Score > 3
3	Structural X-ray changes in the spine	X-ray, mSASSS (syndesmophytes, ankylosis)	Not applicable

axSpA: axial spondyloarthritis; Nr: number; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score

While the ASAS classification criteria (must) require fixed assignments such as an imaging finding plus another symptom or finding and HLA-B27 plus at least two other fulfilled items [10], the diagnosis is individual, i.e. in principle, many combinations of symptoms and findings are possible. It is important to carefully consider the presence or absence of SpA manifestations, to assess and evaluate positive and negative results of diagnostic tests (imaging, laboratory), and to exclude other reasons that may better explain the presenting symptoms (see below). Although the classification criteria may be fulfilled even without evidence of inflammatory or post-inflammatory structural changes in the SIJ and/or SC by imaging, the diagnosis of axSpA should always be critically questioned if the inflammation or the typical post-inflammatory changes cannot be visualized by imaging.

In the early stages of the disease, physical examination and assessments of function and mobility are usually of little help in making a diagnosis. In order to clarify the problems of classification and diagnosis, the individual points are explained in more detail below.

Explanations of the individual building blocks for the diagnosis of axSpA

1. In principle, it is of course possible to diagnose axSpA after 6 weeks of back pain, but this is not possible with the classification. The situation is similar to a "late-onset" clinical picture of axSpA, i.e. the typical symptoms of the disease only began after the age of 45. This does exist [15], but it is comparatively rare. On the other hand, back pain is simply very common (about 20% of the population in Germany suffer or used to suffer from chronic back pain, axSpA is only responsible for about 5% of these cases) and much more often not caused by axSpA [16].

2. With regard to imaging, the diagnosis and classification of AS or axSpA was long based on the New York Criteria [9] definition of definite structural radiographically visible changes in the SIJ, formally divided into grades 0–4, whereby it was considered crucial that at least one grade 2 be present on both sides, and unilateral involvement was sufficient for grades 3 and 4. This rather arbitrarily defined cut-off proved to be less practicable early on [17], but this distinction was maintained for a long time.

With regard to MRI, there were early suggestions from ASAS as to what a "positive" MRI of the SIJ [18] or the SC [19] should look like. The definitions have been updated several times [20–22]. Important for inflammation in the SIJ is evidence of bone marrow oedema (BME) in the subchondral bone in at least 2 layers. However, such changes also occur in the normal population [23] or in runners [24], or in osteitis condensans [25]. Important questions are not only the size of the BME [26], but also its localization (mechanically induced BME occurs predominantly in the ventral/anterior section of the SIJ), or the combination with structural changes, especially erosions, that is common in axSpA but not in mechanically-induced conditions [27]. There are increasing calls to use MRI rather than CR for structural changes in the SIJ as well [28]. Here, as in CR, erosions are the most important changes [27]. For better detection of erosions, special "erosion-sensitive" MRI sequences (such as the fat-saturated T1 gradient-echo sequence) should nowadays be included in routine protocols for MRI of the SIJ. On the other hand, the administration of contrast medium (gadolinium) can be omitted. Low-dose computed tomography (CT) is an alternative for the detection of structural changes in the SIJ [29] but the exposure to ionizing radiation is still considered an ethical problem even though the burden of radiation is now comparatively low.

3. In Central Europe, the prevalence of HLA-B27 in the population is about 8%, while 70–90% of axSpA patients are carriers of at least one *B27* allele [1, 2]. It is thus clear that most people with back pain who are (coincidentally) HLA-B27+ do not have axSpA. This is also supported by data from a blood donor study, which also calculated a prevalence of AS of 0.55% [30]. Nevertheless, HLA-B27 increases the prevalence of AS by at least a factor of 10 in a person with IBP who started before the age of 45 [31]. Furthermore, it plays a role as a parameter for an effective referral strategy in patients with possible axSpA [32]. It is also important in the age of migration that HLA-B27 appears to play a much smaller role in Arab countries [33]. The use of a polygenic risk score, which is not practically available and is used at the moment, may help to optimize the diagnosis of axSpA. However, this seems to be more relevant for r-axSpA [34].

4. C-reactive protein (CRP) is primarily an activity marker and helpful in determining the indication for biologic therapy [35]. The better performance of the axSpA Disease Activity Score (ASDAS) compared to the Bath AS Disease Activity Score (BASDAI) is also due to the fact that the CRP was taken into account in the former [36]. On the other hand, this common inflammatory parameter was elevated in no more than half of the patients with axSpA in cross-sectional studies [37]. This means that a normal CRP does, of course, not exclude the diagnosis of axSpA! Incidentally, this is similar in rheumatoid arthritis or also in psoriatic arthritis (PsA). Here, however, the clinical problem is somewhat simpler because one can see and feel swollen hands, whereas this is not the case with back pain. It is also important to note that 50% of axSpA patients with normal CRP had elevated levels in follow-up examinations [38].

5. IBP, first identified in 1977 [39], is considered particularly typical of patients with axSpA. Slightly modified definitions have since been proposed for it, but they are not essentially different [40, 41]. An early publication [31] had already shown that the specificity of the item "INP" is limited. A large population study showed a frequency of this symptom of 5–6% in the U.S. [42]. The problem is further illustrated when one realizes that the likelihood of axSpA in patients with chronic back pain presenting to an English general

practice was 5% [43]. However, when such a patient complains of IBP, the likelihood of axSpA increases to only 15% [44]. This can be increased significantly, to over 50%, by a positive HLA-B27 test, but even this, as mentioned [31], is not proof of the presence of axSpA.

6. With regard to the presence of extraspinal manifestations, in the vast majority of cases these are anamnestic indications, i.e. there is very rarely the case that such symptoms occur simultaneously with the leading symptom of back pain so that one is dependent on anamnestic indications in this respect. However, these are often uncertain. This is especially true for the symptom of enthesitis, which, as a clinical diagnosis, usually requires reliable imaging such as MRI or ultrasound because physical examination is in most cases neither sensitive nor specific enough. Nevertheless, tendinitis is certainly more common in SpA than in other inflammatory rheumatic diseases [45]. In addition, a reliable diagnosis of enthesitis based purely on history is virtually impossible. Acute dactylitis is also very rarely a leading symptom in patients with chronic back pain. Here, however, it is generally easier for patients to remember a sausage finger or toe, and sometimes there is even a photo on the mobile phone. Overall, these symptoms are of only very limited help in making the diagnosis of axSpA.

7. An already established diagnosis of IBD can help in diagnosing axSpA. This is especially true if an appropriate diagnosis has already been made and there are clear findings. The incidence of IBD in patients with axSpA was in the range of 5–10% in studies, and psoriasis was slightly more common [46, 47]. In contrast, the prevalence of AU in patients with AS is much higher—in the range of 30% [1]. Of interest, therapy with TNFi also had a positive effect on this ocular manifestation in many patients with AS [48]. Psoriasis occurs over time in about 10–15% of axSpA patients, and IBD in about 5–10% [49].

8. The definition of ASAS for a positive family history of SpA includes the following conditions in first or second-degree relatives: AS, AU, reactive arthritis (ReA), IBD, and psoriasis. In two recently studied cohorts, a positive family history of AS or AU was shown to be useful for the diagnosis of axSpA, but this correlated with HLA-B27 positivity. This was not the case for ReA, IBD, or psoriasis [50]. The result suggests that the ASAS definition of a positive family history of SpA should be updated.

9. Especially in the early phase of axSpA, patients respond very well and usually much better than those with other causes of back pain to therapy with non-steroidal anti-inflammatory drugs (NSAIDs)—as first observed over 30 years ago [51]. However, this seems to work less well in patients with longer symptom duration [52]. Therapy with NSAIDs may have an effect on current MRI findings after all, i.e. BME present before therapy was no longer detectable in a retrospective study [53], whereas this was less impressive in an earlier study [54]. In anti-TNF studies, patients in the placebo group were usually treated consistently with NSAIDs. This usually did not show dramatic improvements [55]. Incidentally, medication with NSAIDs seems to be prognostically more favorable in AS patients [4, 5].

10. The exclusion of other diagnoses that better explain the presenting symptoms is now found in many classification criteria. Even if this is not the case with the ASAS criteria, there is little doubt that it would also be useful here. Of course, this is also essential when making a diagnosis. An overview of other causes of back pain and essential differential diagnoses (see below) is shown in a paper published a few years ago [56].

Differentiation between radiographic and non-radiographic axSpA

The ASAS classification criteria have led to the fact that, in addition to the classification as classical AS, which had long been diagnosed on the basis of the New York criteria [8] and is now called radiographic axSpA (r-axSpA), there is also a so-called non-radiographic axSpA (nr-axSpA), which is diagnosed on the more or less arbitrarily defined basis of the presence or absence of definite radiographic i.e. structural changes in the SIJ. AS and r-axSpA are largely congruent [57]. It should be emphasized that this is a distinction that is only meaningful in the context of classification [58]. This artificial, historically more or less accidental distinction makes no sense for making a diagnosis, because the cut-off (definite structural changes in the SIJ X-ray) is, as already mentioned, not reliable [15] and, moreover, allows that nr-axSpA patients can have in the CS such as the typical syndesmophytes.

In summary, for the clinical diagnosis use of the term axSpA is sufficient. There is only one comparatively small problem: almost all biologics are approved for both indications r-axSpA and nr-axSpA—except for infliximab, although the earliest study to date was conducted with this pilot preparation [59], and the first JAK inhibitors (JAKi) tofacitinib.

Several studies in recent years have shown that nr-axSpA does not have a self-limiting course in most cases and that continuous therapy is better than discontinuing the TNFi, with almost half of the patients still showing a good outcome after 6 months of treatment with these bDMARDs and then discontinuing them [60].

Diagnostic clues in the later stages of the disease are based primarily on objective evidence of changes in mobility [61] and functional capacity [62], which are often, but not always, correlated with radiographic changes in the CS [63]. However, their course is heterogeneous [64], with disease activity having a major influence [65]. With regard to the differential diagnosis of syndesmophytes, degenerative osteophytes and similar changes in diffuse skeletal hyperostosis (DISH) have to be considered [25]. Residual conditions after septic inflammatory states can also have an ankylotic appearance [66].

As recently shown, using a patient example observed in real life, there are some open questions regarding the diagnosis of axSpA [67]. These include, for example, the question of whether there are long-term courses of axSpA without there being even a slight structural change. Of course, this discussion also includes the fact that there are considerable differences in the presentation and course between men and women with the disease [68]. However, the e majority of experts doubts whether this makes them two fundamentally different diseases.

Imaging

In the early phase of axSpA disease, MRI of the SIJ is the crucial imaging tool. This involves both inflammatory and structural changes. The combination of both has the best sensitivity and specificity for diagnosis [27]. While there are minor MRI changes reminiscent of inflammation in the SIJ even independent of axSpA [23, 24], erosions in this anatomic location (especially multiple) caused by non-inflammatory disorders are rare but do occur [25].

Recently published reviews [63, 66] have provided an overview of recent publications on the performance of imaging techniques in SpA—such as conventional radiography, MRI, CT, and dual-energy X-ray absorptiometry (DXA) including trabecular bone score (TBS). Typical examples of radiographic changes in the SIJ (Figure 1) and spine (Figure 2) and with CT (Figure 3) in the SIJ and with MRI in the SIJ (Figure 4) and spine (Figure 5) are shown in the figures.

Radiographic progression in the spine is measured in patients with axSpA with the modified Stoke AS Spinal Score (mSASSS), which has limited sensitivity to change in two years and does not take into account the thoracic spine, where most inflammation occurs [69]. There are promising initial results with low-dose CT [70]. Nevertheless, it is also becoming increasingly clear with the mSASSS that continuous inflammation inhibition with TNF blockers also has an effect on radiographic progression. This was also shown in a retrospective study [71] and prospectively, in that radiographic progression decreased in years 3 and 4 compared with years 1 and 2 under TNFi [72]. Positive trends in terms of a low rate of progression were evident under the IL-17 blockade [73]. In an H2H study (SURPASS), no difference was found between adalimumab and secukinumab with respect to radiographic progression in 2 years [74].

Differential diagnoses

Clinically important for the evaluation of patients with axSpA is the fact that back pain can also have other causes than inflammation or new bone formation in the axial skeleton [56, 63, 66]. There are several important differential diagnoses such as the already mentioned osteitis condensans [25] and DISH [75], but also common degenerative CS changes [76] such as in disc degeneration and fibromyalgia [77]. The frequent non-specific low back pain usually does not last longer than 6 weeks - and thus does not fulfill the definition of chronic back pain (> 3 months), but it does not rarely become chronic and relapse [78, 79].

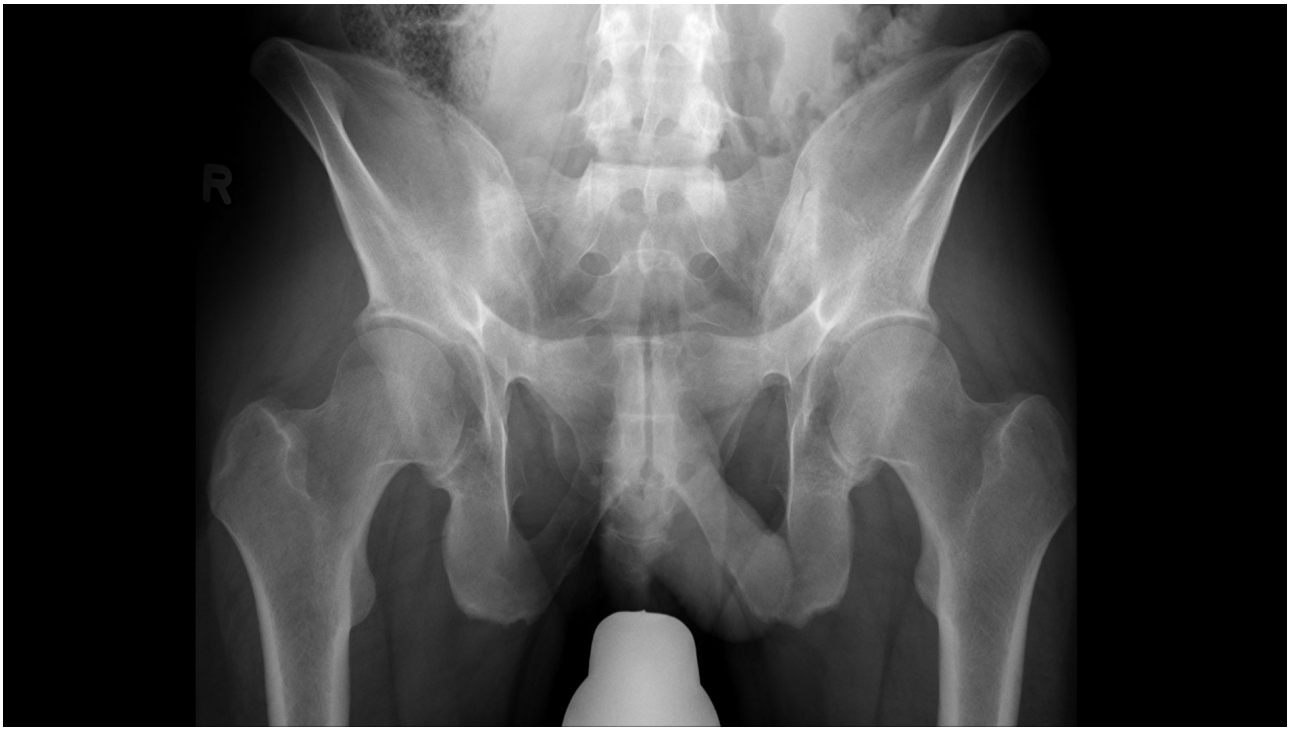

Figure 1. Radiographic changes in the sacroiliac joints. Pelvic X-ray (Ferguson view) of a 42-year-old HLA-B27+ patient with axial spondyloarthritis (axSpA). Right side—ankylosis of the joint space with some sclerosis, left side—joint space is still visible in the cranial part but disappears in the caudal part of the joint (partial ankylosis). This corresponds to radiographic sacroiliitis of grade 4 right and grade 3 left according to the grading system of the modified New York criteria

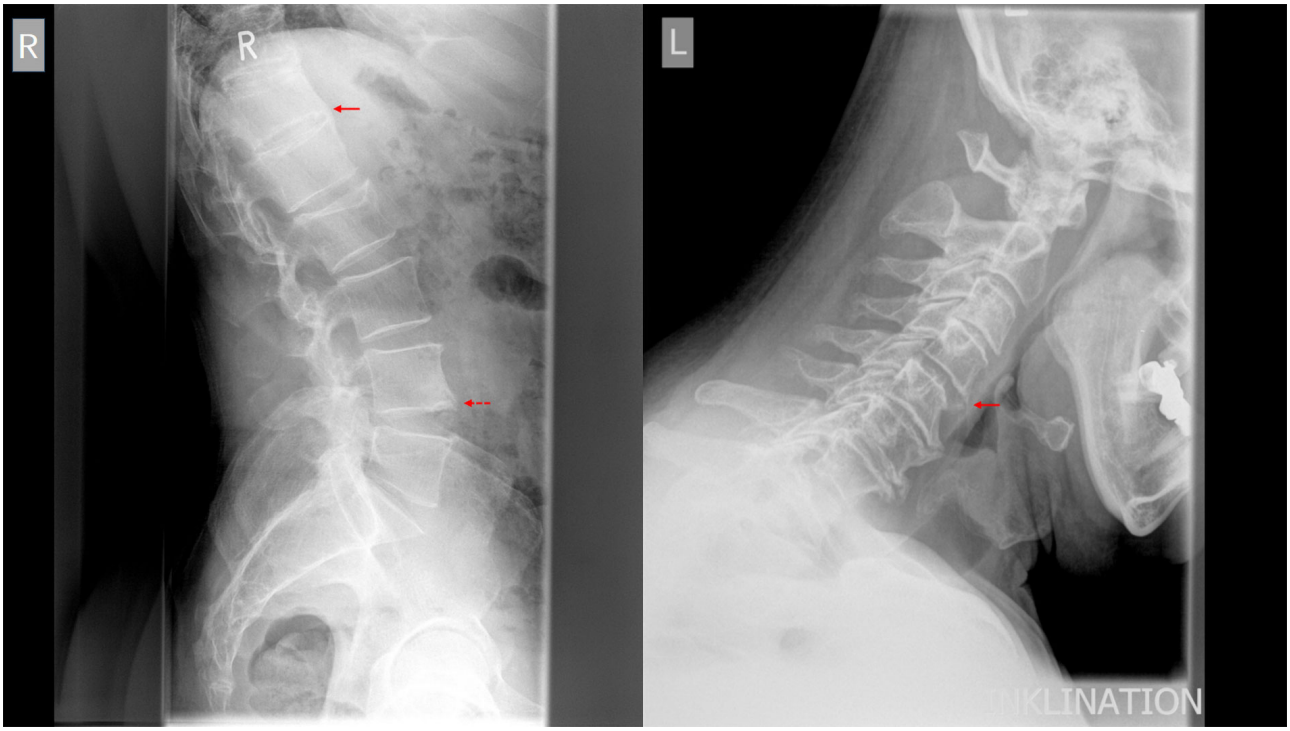

Figure 2. Structural changes in the spine in axial spondyloarthritis (axSpA). Conventional lateral X-ray of the lumbar (R) and cervical (L) spine of a 50-year-old patient with axSpA, showing typical syndesmophytes in the lumbar spine (bridging syndesmophyte—solid arrow, singe syndesmophyte—dotted arrow) and rather mixed changes in the cervical spine (arrow shows a syndesmophytes while new bone formation in the segments below is likely to be of degenerative origin, also note height of the intervertebral spaces)

Axial skeletal involvement in PsA

PsA is now usually included in the group of SpA, although only a proportion of patients have axial skeletal involvement, and many patients present with a picture more akin to RA or even erosive finger joint

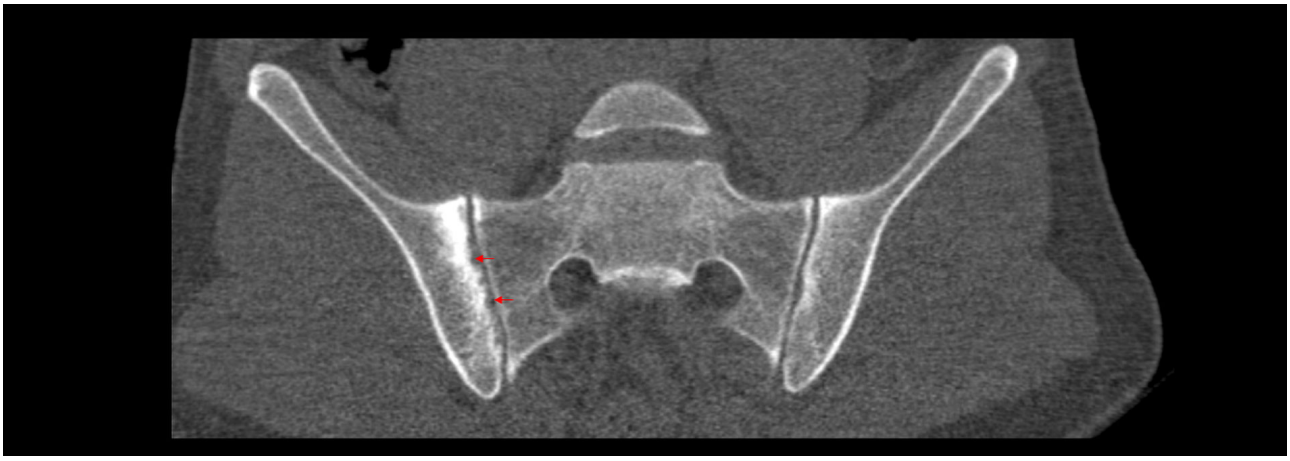

Figure 3. Structural changes on computed tomography (CT) of sacroiliac joints in axial spondyloarthritis (axSpA). The CT scan shows extensive erosive changes (arrows) and sclerosis in the right sacroiliac joint in a 37-year-old patient with axSpA

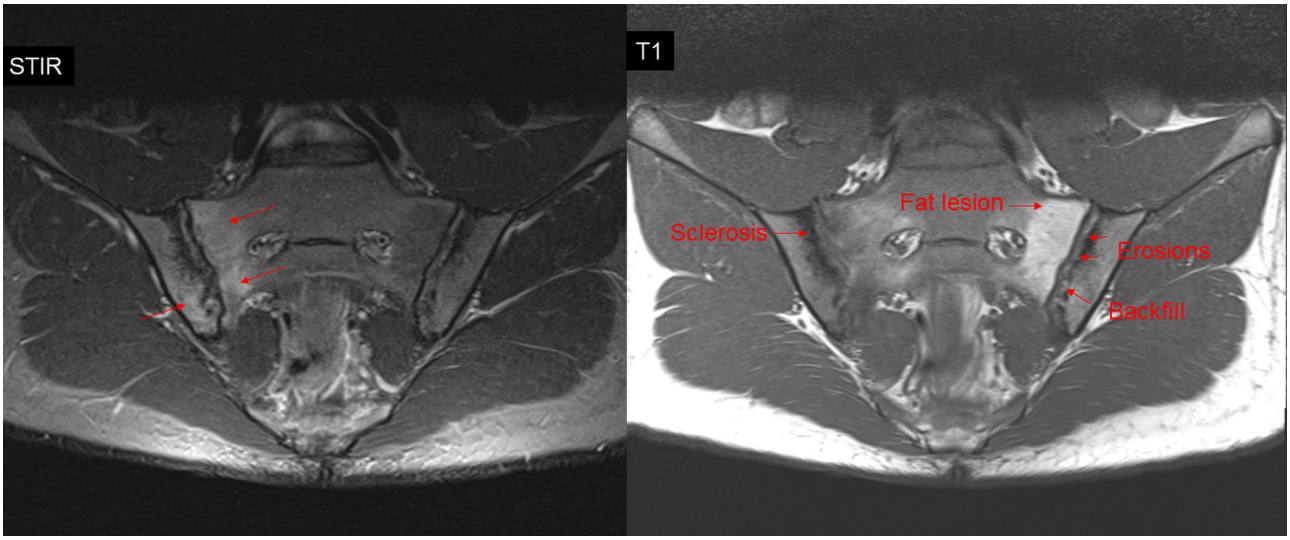

Figure 4. Active inflammatory and structural changes on magnetic resonance imaging (MRI) of sacroiliac joints in axial spondyloarthritis (axSpA). MRI of the sacroiliac joints of a 39-year-old male patient with inflammatory back pain for approximately 12 years, HLA-B27 positivity. The STIR sequence shows extensive subchondral bone marrow edema located in the middle area of the right sacroiliac joint (arrows). The T1 weighted sequence shows subchondral sclerosis, erosions, and fat metaplasia in the erosion cavity (backfill) as well as a fat lesion

osteoarthritis [80]. Nevertheless, in clinical practice, most patients initially have oligoarthritis, while, in contrast, clinical trials usually include patients with polyarthritis [81, 82]. Some patients also have back pain suggestive of axial PsA [82, 83]. Recently, there has been increased discussion about the extent to which so-called axial PsA could represent a special form of axSpA [84]. The discrepancy between the efficacy of anti-IL-23 therapies in PsA versus axSpA plays a role here [85]. In any case, it is certain that HLA-B27 has an influence on the phenotype of axial skeletal involvement in PsA [86].

The role of HLA-B27 in the pathogenesis of axSpA

The pathogenesis of axSpA has not been sufficiently clarified to date. Nevertheless, mechanical factors probably play an important role, at least initially, while a certain genetic predisposition such as through HLA-B27 in combination with T-cell activation is probably decisive for persistence and chronicity [87]. Furthermore, cytokines such as TNFα, IL-17, and IL-23 are of particular pathogenetic significance for the whole group of SpA. With regard to TNFα, there had been convincing results in this regard already some time ago [88]. Indeed, studies with antibodies against these messenger substances have provided clinically relevant results, and several cytokine inhibitors were approved for axSpA and SpA-related diseases.

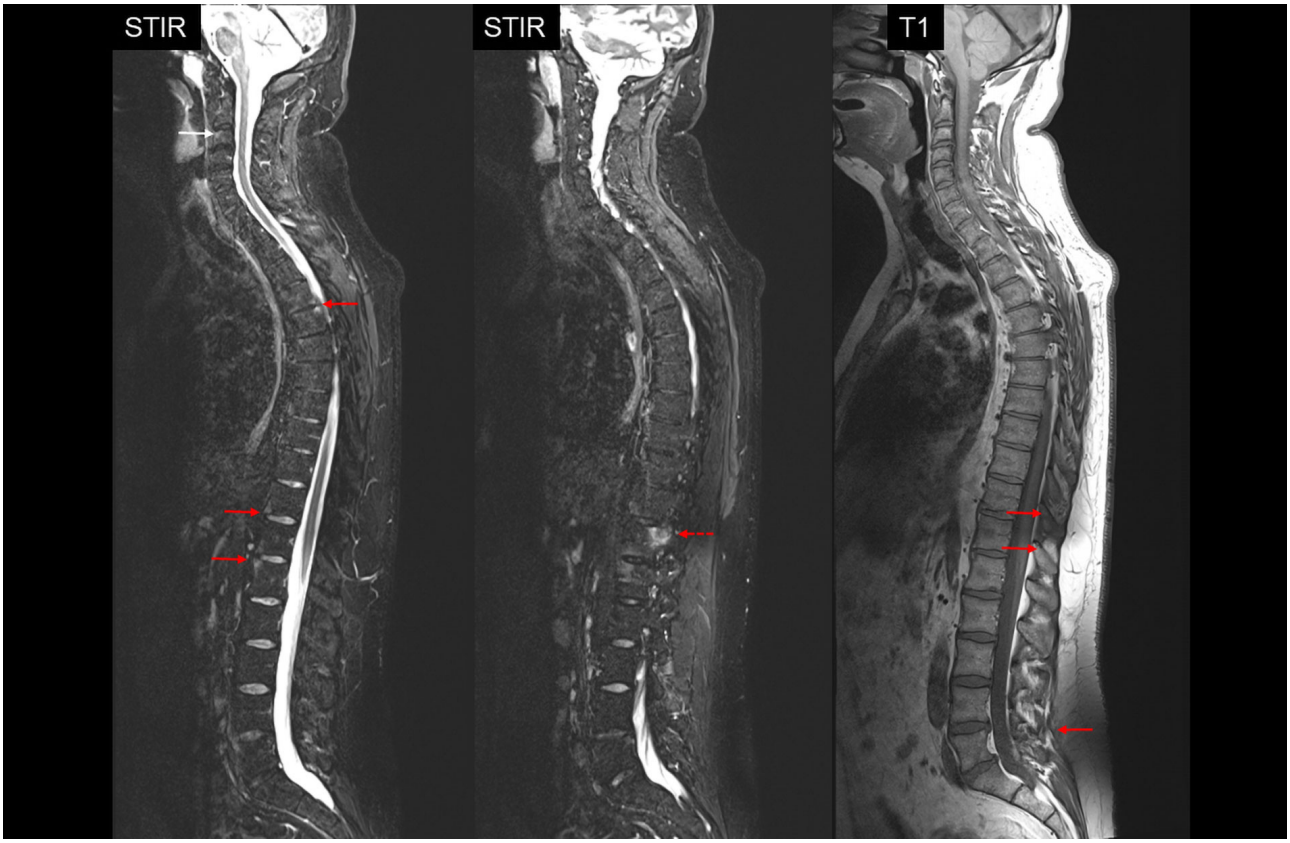

Figure 5. Active inflammatory and structural changes on magnetic resonance imaging (MRI) of the spine in axial spondyloarthritis (axSpA). MRI of the sacroiliac joints of a 52-year-old male patient axSpA. On STIR, active inflammatory changes—spondylitis anterior and posterior are present (solid arrows), as well as highly specific for axSpA arthritis of the costovertebral joint (dotted arrow). T1 shows some fat lesions and possible syndesmophytes (arrows)

However, axSpA is a highly heritable rheumatic disease with a strong association not only with HLA-B27 but also with ERAP-1 and the IL-23 receptor [89]. About 80% of the pathogenesis can be explained by genes but most have not been discovered. The vast majority of alleles (subtypes)—almost 200 have been identified [90] are associated with axSpA but two are not even though they have a rather similar amino acid configuration [91, 92]: *HLA-B2706* (Thailand) and *HLA-B2709* (Sardinia). The physiologic function of HLA-B27 is to present antigenic peptides to CD8 lymphocytes, leading to adaptive immune responses. The "arthritogenic peptide" hypothesis proposes that HLA-B27 presents peptides derived from exogenous microbial sources to CD8 T cells, which may cross-react with self-antigens. Consistent with this theory, an expansion of a restricted pool of CD8+ lymphocytes has been recently found in many axSpA patients but only in a few healthy *HLA-B27* carriers (reviewed in [93, 94]).

The prevalence of HLA-B27 in the Western European population is 6-8% but it is higher in Northern countries and some Indian tribes [87]. Only less than 5% of HLA-B27+ individuals develop axSpA [89], and, in contrast to patients with AS [4, 5], the HLA-B27+ otherwise normal population has a normal mortality rate [95]. Recent studies have shown that a polygenic risk score may provide more information than HLA-B27 testing alone [34]. When using this score major differences between r-axSpA and nr-axSpA patients were found, mainly in females [68]. This is consistent with findings in a large population based study which has revealed differences related to carriage of HLA-B27 in male and female subjects [96]. Indeed, MRI follow-up data showed that the persistence of axial inflammation is especially seen in male axSpA patients [97, 98]. Accordingly, male axSpA patients were shown to consistently develop more structural spinal changes [64, 65]; the reason for this is still not clear.

Conclusions

The current ASAS/EULAR recommendations [99] are based on the treat-to-target (T2T) principle [100]. While for the indication r-axSpA the diagnosis should be certain and increased disease activity (ASDAS >

2.1) must be present, for the indication nr-axSpA in addition either an increased CRP or a positive MRI must be present. Both parameters can also predict a good outcome of treatment with bDMARDs. In the recently published TICOSPA trial [101] the T2T approach was not significantly superior to standard care for the primary outcome, a 30% improvement of the ASAS health index [102], while many secondary efficacy outcomes favored superiority. Furthermore, the safety profile was similar and it was also favorable from a societal health economic perspective. Adding some more patients to both arms would have resulted in a significant p-value even for a 30% improvement of the ASAS HI which had been chosen without experience making an exact sample size calculation difficult [103].

The currently available biologics are called bDMARDs. There are 5 TNFi infliximab, etanercept, adalimumab, golimumab, certolizumab-pegol and several of their biosimilars, as well as 3 bDMARDs directed against IL-17 (secukinumab, ixekizumab, bimekizumab) and two so-called ts DMARDs, the JAKi tofacitinib and upadacitinib, are approved for axSpA and available, two more are approved for other indications (baricitinib, filgotinib). Bimekizumab targets not only IL-17A but also IL-17F which may be an advantage, at least in psoriasis [104].

Finally, it should be mentioned that the publication of the first quality standards for axSpA is also regarded internationally as a great success and progress for the management of affected patients [105]. An important deficit identified in this context is the still too-long delay in diagnosis. Good cooperation between rheumatologists, orthopedic surgeons, and general practitioners is needed here. Good practicable referral systems are needed to ensure sufficient pre-selection—otherwise, the work can quantitatively not be managed.

Abbreviations

AS: ankylosing spondylitis

ASAS: Assessment of Spondyloarthritis International Society

AU: anterior uveitis

axSpA: axial spondyloarthritis

bDMARDs: biologic disease modifying anti-rheumatic drugs

BME: bone marrow oedema

CRP: C-reactive protein

CT: computed tomography

IBD: inflammatory bowel diseases

IBP: inflammatory back pain

IL: interleukin

JAK: Janus kinases

MRI: magnetic resonance imaging

nr-axSpA: non-radiographic axial spondyloarthritis

NSAIDs: non-steroidal anti-inflammatory drugs

PsA: psoriatic arthritis

r-axSpA: radiographic axial spondyloarthritis

SC: spinal column

SIJ: sacroiliac joints

SpA: spondyloarthritides

TNFi: tumor necrosis factor inhibitors

TNFα: tumor necrosis factor alpha

Declarations

Author contributions

JB: Conceptualization, Investigation, Writing—original draft. DP: Writing—review & editing, Investigation, Validation. All authors read and approved the submitted version.

Conflicts of interest

Jürgen Braun, who is the Associate Editor of Exploration of Musculoskeletal Diseases, had no involvement in the decision-making or the review process of this manuscript. The other authors declare that they have no conflicts of interest.

Ethical approval

According to the local guidelines, since this is a review and not a study, no ethical approval is needed in Germany.

Consent to participate

All patients in the University Hospital B. Franklin in Berlin give informed consent.

Consent to publication

All patients in the University Hospital B. Franklin in Berlin give informed consent.

Availability of data and materials

The raw data supporting the conclusions of this manuscript can be requested from the corresponding author for appropriate reasons.

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