Imaging in Axial Spondyloarthritis

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ABSTRACT: Axial spondyloarthritis (axSpA) covers the stage of non-radiographic axial spondyloarthritis (nr-axSpA) and classic ankylosing spondylitis. The pathognomonic findings of axSpA are mainly inflammatory and osteoproliferative changes in the sacroiliac joints (SIJ) and the spine. Various imaging techniques are being used in daily practice for assessment of disease-specific changes, such as periarticular bone marrow edema, erosions, sclerosis, fat metaplasia and ankylosis in the SIJ or spondylitis, spondylodiscitis, facet joint involvement, or syndesmophytes in the spine of patients with axSpA. Conventional radiographs are still considered the gold standard for assessment of structural changes, while the method of for detection of inflammatory changes is magnetic resonance imaging (MRI).

A result for an MRI in the SIJ is considered positive for axSpA when more than one lesion is present on one MRI slice. If there is one lesion only, it should be present on at least two consecutive slices. For the spine, inflammatory lesions should preferably be located in the corner of the vertebral bodies, while occurrence of spondylitis in three or more vertebral corners is considered highly suggestive of axSpA.

This review gives a detailed overview about the benefits and limitations of all available imaging techniques in patients with axSpA, explains the usage of imaging techniques in the context of diagnosis and differential diagnosis of the disease and reports on the potential future trends in the area of imaging of the axial skeleton in patients who are suspicious for this diagnosis.

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KEY WORDS: conventional radiographs, magnetic resonance imaging (MRI), sacroiliac joints (SIJ), bone marrow edema, axial spondyloarthritis (axSpA)

The diagnosis of axial spondyloarthritis (axSpA) covers both stages of one disease: non-radiographic axial spondyloarthritis (nr-axSpA) and classic ankylosing spondylitis (AS) [1]. AxSpA is a chronic inflammatory rheumatic disease that mainly affects the axial skeleton, while patients with predominantly peripheral SpA present mainly from arthritis, enthesitis, and dactylitis [1]. The pathognomonic findings of axSpA are inflammatory, osteodestructive and osteoproliferative changes in the sacroiliac joints (SIJ) and spinal structures, many of which are of entheseal nature.

Sacroiliitis, spondylitis, (abacterial) spondylodiscitis, and spondylarthritis are the main inflammatory manifestations in the axial skeleton, which may lead to new bone formation occurring as syndesmophytes and ankylosis in the vertebral column, while about 15% of AS patients even develop a 'bamboo spine'. These characteristic changes may occur during the course of the disease in many patients. However, the prevalence rates of these manifestations and also the velocity of disease progression and severity are at variance [2]. The whole pathogenesis, and in particular the complex pathogenic process between inflammation and transformation to structural changes in axSpA, is still not completely understood. An outstanding aspect in this regard is the parallel occurrence of inflammation, osteodestruction, and osteoproliferation in addition to osteoporotic changes in the vertebral column.

Different imaging techniques are relevant for diagnosis, classification, assessment of disease activity and structural damage, and prognosis of patients with axSpA. Their capacity to detect the potential pathologies is clearly different. Conventional radiographs are currently still considered the gold standard for assessment of structural changes in the axial skeleton of patients with axSpA [3]. Computed tomography (CT) is useful for the detection of structural changes in the SIJ because of its superior sensitivity and specificity in relation to conventional radiography–especially when the absence of structural changes needs to be documented. However, both methods are unable to visualize active inflammation. The best method to detect inflammatory changes is magnetic resonance imaging (MRI). The use of scintigraphy has not been recommended due to the very low specificity of this technique [4].

The different imaging techniques currently available in axSpA should be used complementarily and according to individual indications.

Only changes in the SIJ are considered relevant in the current classification criteria for axSpA and AS, respectively. Nevertheless, some patients may well show spinal involvement in the absence of pathology in the SIJ [5]. This topic needs further study.

The magnitude of the pathologic changes in the axial skeleton of patients with axSpA is used to quantify inflammatory and structural outcomes of clinical trials in axSpA. Different

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scoring systems have been proposed for the assessment of inflammatory and structural changes in axSpA [6,7].

The prognostic relevance of structural changes (presence of syndesmophytes detected by X-ray) and of the degree of inflammatory changes in the SIJ (detected by MRI in combination with HLA B27) has been well shown [8].

IMPORTANCE OF IMAGING OF THE SACROILIAC JOINTS IN AXIAL SPA

Imaging of the SIJ is critically important for diagnosis and classification of patients with axial SpA because the vast majority of these patients show involvement of this part of the axial skeleton in all but the early stages of the disease. For example, a certain degree of structural changes in the SIJ is a prerequisite for the classification of AS according to the 1984 modified New York criteria [9] and for classification of axSpA according to the Assessment of SpondyloArthritis international Society (ASAS) criteria published in 2009 [1].

CONVENTIONAL RADIOGRAPHY

For the initial approach to a patient under suspicion of axSpA, x-rays are the gold standard for assessment of structural changes in the SIJ. Typical findings are sclerosis, erosions/pseudodilatation, and/or bony bridges. The method used for quantification of structural changes in the SIJ in clinical practice [10] has been derived from the modified New York criteria for classification of AS [9]. Importantly, for this evaluation, the age of the patients needs to be considered because bony changes in the SIJ may be frequently found in older individuals just as a consequence of osteoarthritis. For a diagnosis of axSpA in early disease stages, conventional radiography has limited value because of its poor sensitivity and specificity due to the inability of the method to detect active inflammation [11]. Routine imaging of patients with low back pain to detect chronic SIJ changes has not provided substantial additional information in one study [12] but this may be different in younger patients with inflammatory back pain and a high suspicion of axSpA [5]. There is some evidence that structural changes in the SIJ may develop rather quickly [13].

The pathognomonic findings of axial spondyloarthritis (axSpA) are mainly inflammatory and osteoproliferative changes in the sacroiliac joints (SIJ) and the spine

COMPUTED TOMOGRAPHY

For the detection of structural changes in the SIJ, CT has proven more useful than conventional radiography because of superior multidimensional imaging of anatomic structures in which the SIJ are cut into slices. This method is advantageous because of the complicated anatomy of the sacroiliac joint due to the irregular S-shaped orientation and the partly overlapping sacral and iliac joint structures.

However, for CT, similar to what was said for X-rays, findings of sclerosis, joint space narrowing, erosions, and ankylosis may be misleading in elderly patients since subchondral sclerosis of the SIJ, especially in the iliac part, is a phenomenon of aging similar to joint space narrowing [14].

In general, the radiation exposure of CT technology needs to be considered when deciding on the imaging method to use; therefore, CT is not recommended for the evaluation of low back pain and suspicion of SpA in daily practice.

SCINTIGRAPHY

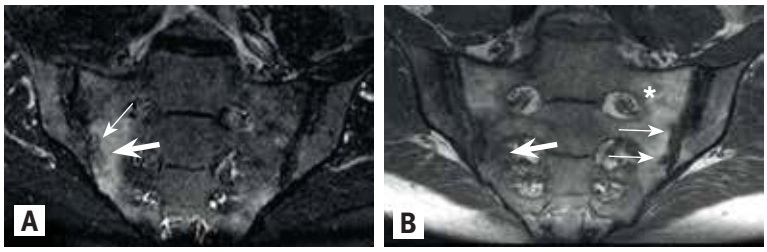
The nuclear medical method of scintigraphy takes advantage of the physical behavior of the radionuclide technetium^{99} that enriches in areas of increased metabolism or inflammation. Therefore, scintigraphy of the SIJ has been frequently used to detect sacroiliac and/or spinal inflammation in patients under suspicion of axSpA in the past. However, since sensitivity and specificity of other imaging techniques such as MRI were shown to be superior, its use has decreased substantially in recent years [4]. Scintigraphy results in the SIJ seem to be more reliable if there is unilateral involvement consistent with clinical symptoms. Therefore, since scintigraphy as a tool to detect sacroiliitis has clear limitations, it is not suitable for making a diagnosis of axSpA. Whether scintigraphy can be of use as a more general tool for detecting enthesitis in different regions at a time remains to be elucidated. Similar to CT, the radiation exposure needs to be considered for the evaluation of young patients who present with low back pain.

MAGNETIC RESONANCE IMAGING

One of the major advantages of MRI is the detailed anatomic and pathologic imaging in connection with the information provided on the localization of inflammation. MRI is especially useful in detecting bone marrow edema as a sign of osteitis in the axial skeleton in patients with axSpA [Figure 1A]. MRI is also able to visualize the complicated anatomy of the region of the SIJ, including characteristic abnormalities of the periarticular soft tissue, which is only indirectly visible by other methods [Figure 1A]. Sacroiliac inflammation, as detected by MRI, has been shown to correlate with conventional histology and immunohistology and to some degree also with clinical symptoms of axSpA [15]. MRI has also been used to detect more chronic structural changes of bone and joints. The typical structural changes in patients with axSpA are periarticular fat deposition, subchondral erosions, sclerosis [Figure 1B] and bony bridges/ankylosis. Especially the fat signal has raised interest because this cannot be detected by conventional X-rays.

Even though structural changes of the SIJ as depicted by MRI are not included in the current ASAS classification criteria [1] and the definition of a positive MRI [16], there is some evidence that lesions such as fatty changes and erosions may contribute to the diagnostic usefulness of MRI in axSpA [17]. However, it

Figure 1. Magnetic resonance imaging (MRI) of the sacroiliac joints of a patient same with ankylosing spondylitis. Bone marrow edema (osteitis) is visible as hyperintense signal in the short tau inversion recovery (STIR) sequence **[A]** and hypointense signal in the T1 weighted sequence **[B]** (thick arrows). Post-inflammatory changes such as fat deposition is visible as hyperintense signal in T1 and hypointense signal in STIR (asterisk). Structural changes (erosions) are seen in both sequences (thin arrows). In this case of more than one inflammatory lesion per slice, the MRI is highly suggestive of axial spondyloarthritis



is not clear whether MRI can substitute for radiography to optimize the diagnosis of chronic changes, and also an international agreement on clear-cut definitions has not been achieved to date.

Importantly, and in contrast to other imaging techniques, MRI is not associated with radiation exposure. This makes this technique especially favorable in young patients, especially women, children, and patients with a past or expected history of relevant radiation exposure. However, routine access to MRI, optimal technical equipment, and a skilled staff is not widely available and the costs of MRI are still higher than other imaging techniques. Furthermore, claustrophobia, pacemaker implantation, and metal implants are relative contraindications for performing MRI. In addition, the long duration of the procedure (approximately 20–30 minutes) makes the technique not applicable for some patients because of intolerable pain and stiffness in the supine position.

Conventional radiographs are still considered the gold standard for assessment of structural changes, while the method of for detection of inflammatory changes is magnetic resonance imaging (MRI)

DEFINITION OF A POSITIVE MRI OF THE SIJ IN AXSPA

According to the ASAS definition, periarticular bone inflammation seen as hyperintense/inflammatory signal in the bone marrow near the SIJ should be preferably located in the periarticular region. An MRI result is considered positive for the SIJ in patients with axial SpA when more than one lesion is present on one MRI slice. However, if there is one lesion only, this should be present on at least two consecutive slices [16] [Figure 1]. Due to the fact axSpA is a chronic disease that progresses constantly, the chronic and structural changes also play an important role in the identification of these patients in daily practice. However, due to the lack of data about their diagnostic value, structural changes are still not included in the definition of a positive MRI result of the SIJ. In an update, the ASAS/MRI working group included structural damage lesions as an 'add-on' that may contribute to a decision as to whether inflammatory lesions are genuinely due to SpA [18]. In this update, erosions of the SIJ were specifically considered as important to enhance the confidence of classification to axSpA, followed by fat metaplasia and sclerosis, when not explained by other reasons such as age-related changes of the bone marrow or differential diagnostic considerations such as osteitis condensans.

DIFFERENTIAL DIAGNOSES FOR INVOLVEMENT OF THE SIJ

Bone marrow edema is not a specific feature of axSpA and may also occur in other diseases. The most important differential diagnoses for active changes in the SIJ are septic sacroiliitis, osteitis condensans, and pelvic fractures. Others include chronic changes, extensive sclerosis, or structural changes due to degenerative conditions.

In the case of septic sacroiliitis, conventional radiographs are usually normal in the first weeks of disease [14], while MRI is capable to demonstrate the pathology much earlier according to Stürzenbecher et al. [19]. Therefore, MRI is considered the gold standard for a diagnosis of septic sacroiliitis. The major differential diagnostic criterion is that the infection passes the mark of anatomical borders such as that the proximal parasacroiliac structures including the iliopsoas muscle may be infiltrated. Fractures are mainly seen as insufficiency fractures and are characterized by a bone marrow edema that may be similar to what is seen for sacroiliitis.

An MRI finding of extensive sclerosis, especially at the iliac side of the SIJ, may also be misleading. Osteitis condensans ilii, characterized by a triangular shaped sclerosis, is often found in women after pregnancy [20], but it may occur in men, although rarely. In diffuse idiopathic skeletal hyperostosis (DISH, Forestier´s disease), the typical findings are irregularly shaped SIJ, including sclerosis, ossification of the joint capsule and bony bridges, many of which may be difficult to differentiate from axSpA. However, such changes usually do not occur in young patients.

IMAGING OF THE SPINE IN AXIAL SPA

Spinal changes, usually representing more advanced stages of the disease, may be clinically relevant for a diagnosis of axSpA but they have never been part of classification criteria for AS or axSpA because only 3–5% of patients with AS were reported not to have unequivocal structural changes in the SIJ [21]. The other reason is the similarity of syndesmophytes with spondylophytes of degenerative nature, especially in patients with longer disease duration.

Therefore, the current clinical significance of syndesmophytes is for a diagnosis of axSpA in individual patients with indefinite findings in the SIJ. Furthermore, syndesmophytes

have definite prognostic value since the presence of one syndesmophyte has been shown to increase the risk for the development of more such changes significantly [3]. How much time is needed until structural lesions of the spine develop is not clearly known. Within the first 16 years of AS, bony changes have been reported to be present in more than 50% of the patients [22].

Both inflammatory and structural spinal changes play an important role in the evaluation of medical interventions, since the effect of anti-inflammatory agents such as non-steroidal anti-inflammatory drugs or TNF blockers on spinal inflammation (bone marrow edema) and new bone formation (syndesmophytes) are relevant 'objective' outcomes in clinical studies with axSpA patients. However, clinical symptoms including pain, stiffness and function are considered even more important.

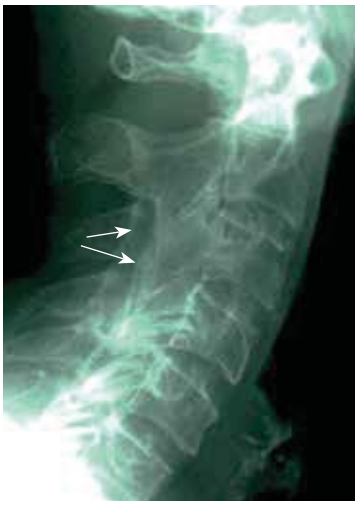


Figure 2. The lateral parts of the vertebral bodies and facet joint area are frequently affected in ankylosing spondylitis, showing typical osteoproliferative changes such as ankylosis (arrows).

CONVENTIONAL RADIOGRAPHS

Similar to conventional radiography of the SIJ, X-rays have a low sensitivity to detect spinal inflammation such as spondylitis, spondylarthritis, or spondylodiscitis [23]. Nevertheless, conventional radiographs are the gold standard for the assessment and quantification of structural spinal changes. The visualization of osteodestructive and osteoproliferative processes in the vertebral bodies is useful to assess the course of the disease and the damage that has already occurred. Spinal changes related to axSpA can be differentiated in osteodestructive (erosions), and hyperproliferative (enthesophytes, vertebral squaring, disc calcifications, spondylophytes, syndesmophytes, bony bridging, vertebral ankylosis) pathologic changes. Syndesmophytes are characterized by their typical vertical growth, which may lead to bridging phenomena in the prediscal region between the intervertebral disc and the anterior intervertebral ligament [24].

More advanced and sophisticated imaging techniques, such as PET in combination with CT, MRI, or whole-body MRI may be used for assessment of axSpA in the future

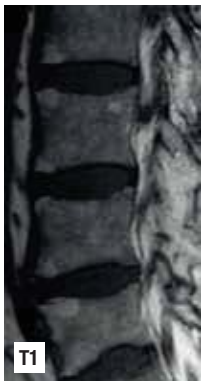
Furthermore, the lateral parts of the vertebral bodies and the facet joint area deserve attention since they are frequently affected in AS [Figure 2]. Since these areas are difficult to assess by most imaging procedures, involvement of the facet joints is frequently underdiagnosed. Ankylosis of the facet joints may be discordantly associated with the presence of bridging syndesmophytes in established AS [25], suggesting that the these joints are primarily and early involved in the course of the disease.

MAGNETIC RESONANCE IMAGING

Also for the spine, MRI is considered the most sensitive method for the detection of inflammatory lesions related to axSpA [26]. Assessment of spinal inflammation on MRI can be used as an indicator of disease activity, as a response tool for biologic treatment, and as a possible predictor of response to therapy [27]. Overall, spinal MRI performs best in the identification and quantification of active spinal lesions [Figure 3A], where it has proven to be superior when compared to other imaging techniques [26]. T1-weighted MRI has also been successfully used to assess structural changes [Figure 3B] [26].

Typical findings of disease activity when using spinal MRI in patients with axSpA are spondylitis, inflammation of the facet joints, and (abacterial) spondylodiscitis.

Spondylitis is a pathognomonic sign of bone marrow edema related to axSpA and has been considered as an early sign of spinal involvement by the disease. It represents an active osteitis and enthesitis at the junction of the annulus fibrosus and the longitudinal ligaments with the anterior ligament, the vertebral body, and the intervertebral disc. When using MRI, spondylitis is typically seen as a hyperintense signal in short tau inversion recovery (STIR) or T1/Gd-DTPA (gadopentetate dimeglumine) sequences with a corresponding hypointense signal in T1-weighted sequences. In later stages, the pathologic signal is inverted as a sign of a healing process and local tissue metaplasia with occurrence of fatty lesions, showing hyperintensity in T1-weichted images and hypointensity in STIR



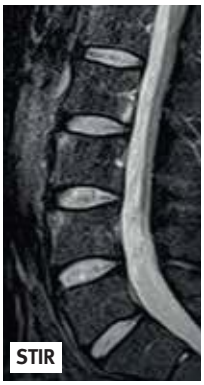


Figure 3. [A] Positive magnetic resonance imaging (MRI) of the spine for inflammatory changes, highly suggestive for axial spondyloarthritis (axSpA), with three vertebral corners being affected by bone marrow edema

[B] Positive MRI of the spine for chronic changes, highly suggestive for axSpA, with several vertebral corners being affected by fatty degenerative changes

(or T1/Gd-DTPA) sequences. There is evidence that the posterior vertebral edges are more frequently involved in early stages of AS [28].

Inflammatory lesions in the facet joints are also characterized by hyperintense signals in MRI sequences sensitive to depict inflammation and hypointense signals in T1-weighted MRI. Active and structural changes of facet, and especially of costosternal and costovertebral joints in AS, may lead to a reduced chest expansion, which is a relatively frequent finding even in young AS patients. If clearly pathologic (age does have an influence on thoracic excursion), MRI can even been used as a diagnostic sign in AS [9].

Abacterial spondylodiscitis is characterized by a circumscribed hemispherical erosive lesion, which is often surrounded by an area of bone marrow edema in one of two adjacent vertebral bodies. In contrast to conventional radiographs, where only the consequences of spondylodiscitis are visible in later disease stages as areas with sclerosis, MRI is able to detect such changes already in early phases [29]. Accordingly, negative radiographic findings are sometimes accompanied by positive MRI findings indicative of spondylodiscitis [29]. Asymptomatic spondylodiscitis may occur in multiple spinal segments in approximately 8–15% of the patients in AS, while a prevalence of such findings was found in up to 31% of patients with enteropathic SpA [30].

DEFINITION OF A POSITIVE MRI OF THE SPINE IN AXSPA

According to the ASAS definition of a positive MRI of the spine in axSpA [31], bone marrow edema should be preferably located in the corner of the vertebral bodies. Evidence of anterior/posterior spondylitis in three or more vertebral corners is considered as highly suggestive of axSpA [Figure 3A], especially in patients of younger ages when degenerative changes play a minor role for a differential diagnosis. Regarding chronic changes, fatty depositions at several vertebral corners may also be indicative of axSpA (Figure 3B). Detection of fatty deposition at vertebral corners, particularly if present at several sites, increases the likelihood of axial SpA, especially in younger patients, and is also associated with future radiographic progression at the affected vertebral edges [32]. There is limited information on the appearance of bone changes in early phases of DISH.

Bone marrow edema is not a specific feature of axial spondyloarthritis (axSpA) and may also occur in other diseases

DIFFERENTIAL DIAGNOSES FOR INVOLVEMENT OF THE SPINE

Similar to the SIJ, bone marrow edema of spinal structures is not specific for axSpA but may also occur in other diseases. The most important differential diagnoses are degenerative changes, blood vessels and hemangioma, fractures, bacterial inflammation, and hyperproliferative changes due to other conditions.

Degenerative changes are seen on X-rays as osteophytes that grow to a horizontal direction (spondylophytes) [3]. The most typical degenerative changes on MRI are the so-called erosive osteochondrosis or Modic lesions, which are frequently associated with chronic back pain in patients of all ages. These changes are recognized by bone marrow edema of the vertebral endplate accompanied by a decreased disc height. Similarly, Scheuermann´s disease starting in childhood is characterized by irregularities in the upper or lower part of the vertebral endplates and erosive changes on the vertebral surface, which are often not recognized before adulthood.

Diffuse idiopathic skeletal hyperostosis (DISH, Forestier´s disease) is characterized by bulky osteophytes, which often exceed the length of the anterior longitudinal ligament. The differentiation between AS and DISH regarding the typical ankylosing processes in both diseases is sometimes difficult. Nevertheless, a radiographic differentiation between AS and DISH is possible, since the shape of the spinal osteophytes differs. While the typical syndesmophytes are much more frequent in AS, DISH is characterized by degenerative spondylophytes and spondylosis [33].

Blood vessels are visualized by hyperintense signals in STIR signals and hypointense signals in T1-weighted MRI sequences. They appear mainly in the posterior part of the vertebral body. A hemangioma is defined as an accumulation of blood vessels typically located within the vertebral body. Although its MRI appearance is similar to that of inflammatory bone marrow edema, these findings represent physiologic abnormalities and do not represent inflammatory changes. In contrast, typical for bacterial spondylodiscitis, the most important inflammatory differential diagnosis is the extension of the hyperintense signal to the surrounding soft tissue crossing anatomical borders. Finally, due to an underlying osteoporosis in association with a rigid stiffness of the spine, a several fold increase in the risk of spinal fractures in patients with established AS has been reported, especially in patients with long disease duration and high degree of spinal involvement [34]. Spinal fractures in AS occur most frequently in the cervical spine but also in the cervicothoracic and thoracolumbar spine, often due to hyperextension injuries [35]. Because of low bone mineral density and severe ankylosis, non-displaced spinal fractures may not be easily diagnosed by conventional X-rays. The shear forces resulting from spinal movements may lead to dislocation of the injured spinal segment [36]. A spinal CT is necessary to diagnose a possible dislocation in patients with persistent or progressive symptoms after injury. Acute fractures show an increased signal intensity on STIR-weighted MRI and variable enhancement in T1/Gd-DTPA MRI, which indicates the location of the fracture line though the vertebral body. On T1-weighted MRI the fractures display a decreased

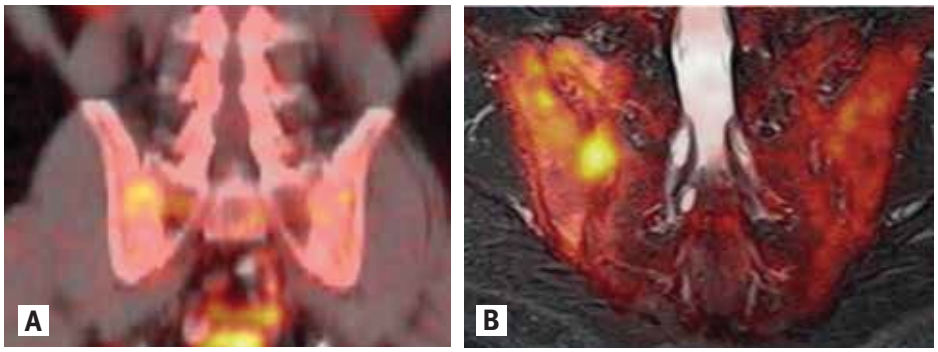


Figure 4. Positron-emission tomography (PET) in combination with computer tomography (PET-CT; 4A used with fluoro-2-deoxy-D-glucose [^{18}F-FDG]) or magnetic resonance imaging (PET-MRI; 4B used with ^{18}F-labeled fluoride [^{18}F-F]). Due to the available tracers used in these examinations, PET-CT is able to detect inflammatory activity **[A]** while PET-MRI can also show metabolic processes such as osteoblastic activity **[B]** which is associated with future ankylosis of the involved structures in patients with axial spondyloarthritis (axSpA).

signal intensity [35]. Finally, a disruption of the anterior longitudinal ligament is detected as a discontinuation and step-off of the low signal intensity structure along the anterior side of the vertebral body.

CAUDA EQUINA SYNDROME

The cauda equina syndrome (CES) is a rare but typical feature in patients with AS that occurs mainly in patients in advanced disease stages. The pathophysiologic basis are cysts of the dural sack. Clinically, these cysts may cause nerve compression symptoms such as irradiating pain and limb numbness. The ultimate cause of CES in AS is not completely known but arachnoiditis due to inflammation of the posterior facet joints leading to adhesions within the thecal sac seems to be a likely explanation. CES is characterized by slow and progressive sensomotoric loss possibly leading to sphincter disturbances and incontinence. The overall prevalence of neurologic symptoms in AS patients is in the range of 2.1%, and CES is not an infrequent cause of these.

Since a diagnosis of CES by conventional radiographs is impossible, CT and MRI which are both able to show enlargement of the caudal sac and the dorsal arachnoid diverticula need to be performed [37].

FUTURE DIRECTIONS

In the future, more advanced and sophisticated imaging techniques, such as positron-emission tomography (PET) [38] in combination with CT or MRI [Figure 4] or whole-body MRI [39] may be used for assessment of inflammatory or detailed structural abnormalities or metabolic processes of the bone structures in patients with axSpA. They may be used in clinical studies and also possibly in daily practice for a precise quantification of the entire spectrum of processes that are involved in the progression of the disease. Furthermore, automated techniques for evaluation of the volume, signal intensity and extent of the relevant lesions are being developed, although such techniques still need to prove that they are able to differentiate between pathologic lesions and possible local anatomic tissue abnormalities or artefacts to avoid false positive or false negative scoring results.

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Capsule

Cytoplasmic p53 couples oncogene-driven glucose metabolism to apoptosis and is a therapeutic target in glioblastoma

Cross-talk among oncogenic signaling and metabolic pathways may create opportunities for new therapeutic strategies in cancer. Mai and colleagues showed that although acute inhibition of EGFR-driven glucose metabolism induces only minimal cell death, it lowers the apoptotic threshold in a subset of patient-derived glioblastoma (GBM) cells. Mechanistic studies revealed that after attenuated glucose consumption, Bcl-xL blocks cytoplasmic p53 from triggering intrinsic apoptosis. Consequently, targeting of EGFR-driven glucose metabolism in combination with pharmacological stabilization of p53 with the brain-penetrant small molecule idasanutlin resulted in synthetic lethality in orthotopic glioblastoma xenograft models. Notably, neither the degree of EGFR-signaling inhibition nor genetic analysis of EGFR was sufficient to predict sensitivity to this therapeutic combination. However, detection of rapid inhibitory effects on [^{18}F]fluorodeoxyglucose uptake, assessed through noninvasive positron emission tomography, was an effective predictive biomarker of response *in vivo*. Together, these studies identify a crucial link among oncogene signaling, glucose metabolism, and cytoplasmic p53, which may potentially be exploited for combination therapy in GBM and possibly other malignancies.

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Eitan Israeli

"Every time I see an adult on a bicycle, I no longer despair for the future of the human race"

Herbert George Wells, (1866–1946), best known as H.G. Wells, English writer. He is best remembered for his science fiction novels. His most notable science fiction works include *The Time Machine* (1895), *The Island of Doctor Moreau* (1896), *The Invisible Man* (1897), and *The War of the Worlds* (1898).