ORIGINAL INVESTIGATIONS

Search for significant clinical and imaging criteria for the differential diagnosis of axial spondyloarthritis and axial psoriatic arthritis

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Objective: to identify a set of criteria for the differential diagnosis of axial spondyloarthritis (axSpA) and axial psoriatic arthritis (axPsA).

Material and methods. *A total of 222 patients were examined: 108 with axSpA (Group 1) and 114 with axPsA (Group 2). Group 1 included patients meeting the axSpA criteria; Group 2 included patients with PsA who had axial involvement and met the CASPAR criteria. Axial involvement was diagnosed in the presence of radiographically definite (rd) sacroiliitis (SI), i.e., bilateral SI grade ≥II or unilateral SI grade ≥III, or active SI on magnetic resonance imaging, or ≥1 syndesmophyte in the cervical spine (C-spine) and/or lumbar spine. Inflammatory back pain (IBP) was defined according to the ASAS criteria. Radiographs of the hands and feet were performed. A multivariate analysis method was used (classification tree construction).*

Results and discussion. *Patients with axPsA were characterized by onset of back pain after the age of 45 years, the presence of polyarthritis with a tender joint count >5 and a swollen joint count >3, dactylitis, skin and nail psoriasis, osteolysis, joint ankylosis, extra-articular bone proliferation, and multiple erosions. Distinctive features included syndesmophytes in the cervical spine, asymmetric, non-bridging, bulky syndesmophytes, spinal changes in the absence of SI, and the presence of rdSI that developed without IBP. Patients with axSpA were characterized by a younger age (<40 years) at diagnosis, presence of IBP, spinal involvement without peripheral arthritis, heel enthesitis, uveitis, inflammatory bowel disease, family history of SpA, HLA-B27 positivity, and the presence of rdSI and sacroiliac joint ankylosis.*

Conclusion. *Classification tree construction made it possible to determine that the differential diagnosis is based on features such as the presence or absence of psoriasis in combination with peripheral symptoms (joint swelling, severe arthralgia) and radiographic signs of osteolysis.*

Keywords: *axial spondyloarthritis; axial psoriatic arthritis; differential diagnosis; clinical and imaging criteria.*
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SpondyloarthritidesF (SpA) are a group of chronic immune mediated inflammatory rheumatic diseases characterized by involvement of the axial skeleton, peripheral manifestations (enthesitis, arthritis, dactylitis), as well as extra skeletal manifestations (uveitis, inflammatory bowel disease [IBD], psoriasis), and are associated with carriage of the HLA B27 antigen [1].

Axial spondyloarthritis (axSpA) is characterized by predominant involvement of the spine and sacroiliac joints (SIJs) [2]. At present, a formal definition of axial psoriatic arthritis (axPsA) is lacking.

AxSpA/ankylosing spondylitis (AS) and psoriatic arthritis with axial involvement (axPsA), as conditions within the spectrum of spondyloarthritis (SpA), share overlapping clinical, imaging, and genetic features [3]. At the same time, recent studies have identified significant differences between axSpA and axPsA [3], suggesting that these represent two distinct diseases [4].

The growing interest among clinicians in the differential diagnosis of axSpA and axPsA is driven by the broader therapeutic options available for psoriatic spondylitis compared with axSpA. In particular, evidence has emerged for the efficacy of interleukin 23 inhibitors (IL 23i), including guselkumab [5] and risankizumab [6], in improving symptoms of axial involvement in PsA, whereas randomized controlled trials have demonstrated a lack of efficacy of this drug class in AS [7]. Therefore, accurate differentiation between these conditions is critically important for practicing rheumatologists to optimize personalized targeted therapy.

However, a multicenter real world study evaluating the diagnosis and management of patients with axPsA (NiSaXPA) [8] revealed substantial diagnostic challenges that adversely affected treatment selection. Central expert review demonstrated initial overdiagnosis of axPsA in 40% of patients. Conversely, underdiagnosis of axial involvement may also occur in routine rheumatologic practice due to incomplete imaging assessment of patients.

These issues are primarily related to the absence of a unified definition and validated diagnostic criteria for axPsA [9], whereas diagnostic criteria for axSpA were clearly formulated by the ASAS (Assessment of SpondyloArthritis International Society) expert group in 2009 [10]. In some studies [11], criteria developed for axSpA [10] have been applied to the diagnosis of axPsA. However, according to our data [12], 45% of patients with axPsA do not meet these criteria.

Diagnostic difficulties in axPsA are further compounded by the possibility of a paucisymptomatic course of axial disease: back

pain may be absent in 25–50% of patients [13]. In such cases, imaging modalities play a central role in the diagnosis of psoriatic spondylitis [14]. Nevertheless, real world practice suggests that rheumatologists primarily rely on inflammatory back pain rather than imaging findings [8].

It should also be noted that current treatment recommendations for axPsA [15,16] are largely extrapolated from clinical trials and guidelines for axSpA [17]. Thus, the diagnosis of spondylitis in PsA remains ambiguous, and early differential diagnosis between axPsA and axSpA may have important therapeutic implications [9]. To optimize the management of psoriatic spondylitis, the development of a dedicated algorithm for the differential diagnosis of axPsA and axSpA is required.

Objective of the study was to identify clinical and imaging relevant features of axial psoriatic arthritis (axPsA) and axial spondyloarthritis (axSpA) and to determine a set of criteria for their differential diagnosis.

Material and Methods. The study included 222 patients with a disease duration of up to 10 years who consecutively sought inpatient care at the V.A. Nasonova Research Institute of Rheumatology from March 2022 to February 2024 and provided written informed consent for participation. The study was approved by the local ethics committee of the V.A. Nasonova Research Institute of Rheumatology (protocol No. 02, dated 27 January 2022).

Patients were divided into two groups: 108 patients with axSpA comprised group 1, and 114 patients with axPsA comprised group 2. Patients in group 1 fulfilled the ASAS classification criteria for axSpA [10]. Patients in group 2 met the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria [18] and had at least one imaging sign of axial involvement: radiographically definite (RD) sacroiliitis, defined as bilateral sacroiliitis of grade ≥ II or unilateral sacroiliitis of grade ≥ III according to the Kellgren grading system; or active sacroiliitis on magnetic resonance imaging (MRI); and/or ≥1 syndesmophyte (paraspinal ossification) in the cervical and/or lower thoracic–lumbar spine; and/or ankylosis of the facet joints of the cervical spine.

All patients underwent a standard rheumatologic assessment [19]. The presence of inflammatory back pain (IBP) was evaluated according to the ASAS criteria [20]. Spinal pain lasting >3 months that did not meet ASAS criteria was classified as chronic back pain (CBP).

Conventional radiography of the pelvis, cervical spine, thoracolumbar spine, hands, and feet was performed using standard techniques. In the absence of radiographically definite sacroiliitis (RD SI), magnetic resonance imaging (MRI) of the sacroiliac joints (SIJs) was performed using a Philips Multiva 1.5 T scanner.

Active sacroiliitis was diagnosed on STIR sequences when bone marrow edema (BME) was detected in the subchondral regions of the SIJs on at least two consecutive slices or when ≥2 BME lesions were present on a single slice [21].

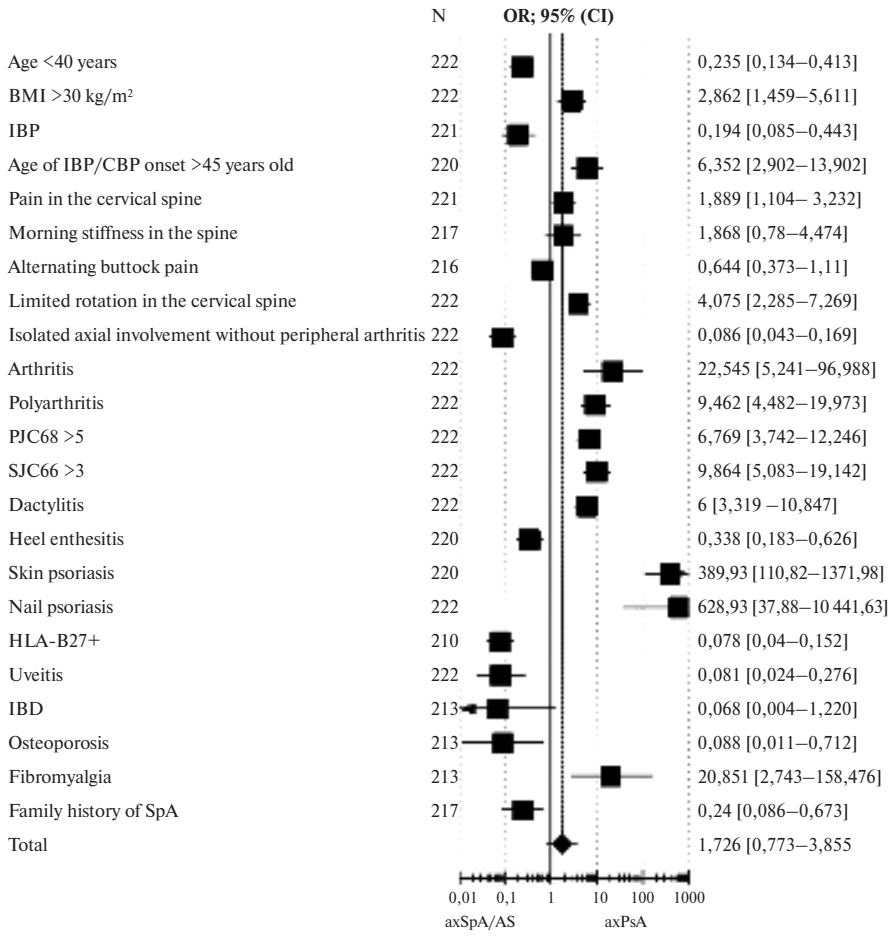

Fig. 1. *Significant clinical and diagnostic characteristics of axSpA and axPsA. PA – peripheral arthritis*

Radiographic signs of spinal involvement included the presence of ≥1 syndesmophyte (paravertebral ossification) in the thoracolumbar and/or cervical spine and/or ankylosis of the facet joints of the cervical spine. Syndesmophytes were characterized as symmetric or asymmetric, bridging or non bridging, bulky ("non marginal") or thin ("marginal"). The proportion of patients with isolated spinal involvement without sacroiliitis was also determined.

Imaging findings were independently assessed by two experts—a radiologist blinded to clinical data and a rheumatologist. HLA class I antigen typing was performed in 187 patients using polymerase chain reaction (PCR)–based methods.

Statistical analysis was performed using the Statistica 10 software package (StatSoft Inc., USA). The following statistical tests were applied: the Pearson χ^2 test for categorical variables, and Student's t test and the nonparametric Mann–Whitney U test for continuous variables.

Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and are displayed using forest plots. Classification trees were constructed using the CART algorithm developed by L. Breiman et al.; improvement in model fit was assessed using the χ^2 measure.

Results. In group 1, there were 62 men (57.4%) and 46 women (42.6%), with a mean age of 35.5 ± 10.8 years; in group 2,

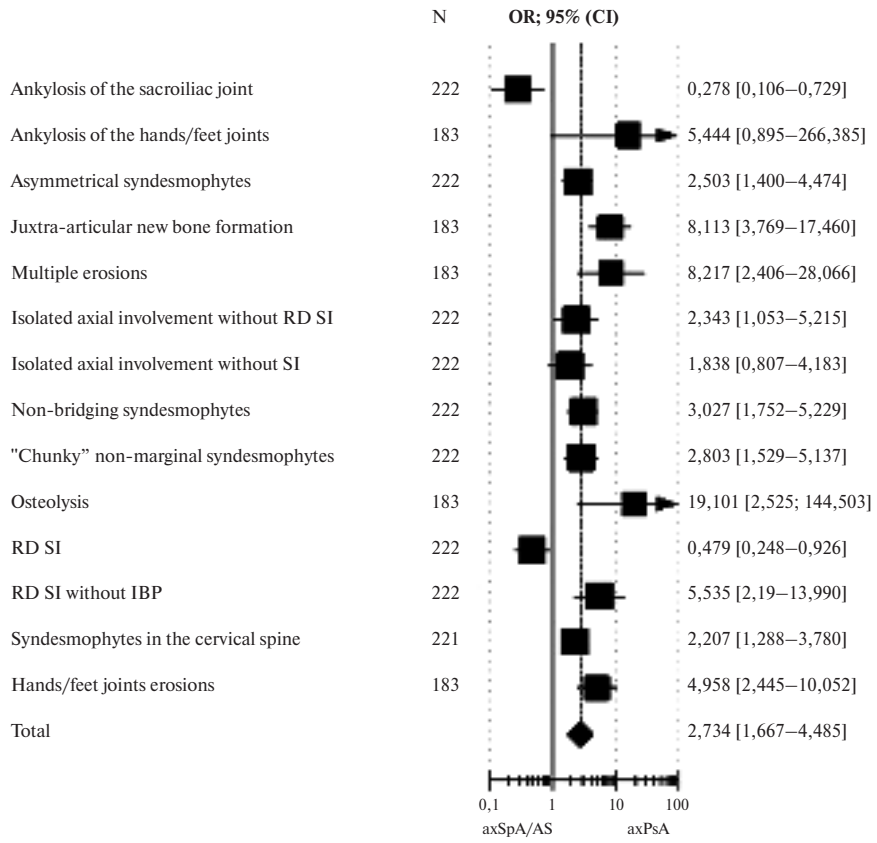

Fig. 2. *Significant radiographic signs of axSpA and axPsA*

there were 58 men (50.9%) and 56 women (49.1%), with a mean age of 46.1±11.6 years.

The baseline characteristics of patients in both groups are presented in our previous publication [19]. Figure 1 shows the results of the assessment of the significance of clinical characteristics associated with axSpA/AS or axPsA.

As shown in the graph, axial psoriatic arthritis (axPsA) is characterized by the onset of inflammatory or chronic back pain (IBP/CBP) after the age of >45 years; the presence of pain and restricted rotation in the cervical spine; polyarthritis with a tender joint count (TJC) >5 and a swollen joint count (SJC) >3; dactylitis; and cutaneous and nail psoriasis.

In patients with axPsA, a body mass index (BMI) >30 kg/mI and concomitant fibromyalgia were observed significantly more often than in axSpA.

A diagnosis of axial spondyloarthritis (axSpA) is most likely in younger patients (<40 years) in the presence of inflammatory back pain, alternating buttock pain, isolated spinal involvement without peripheral arthritis, heel enthesitis, uveitis, inflammatory bowel disease (IBD), osteoporosis, a family history of spondyloarthritis, and HLA B27 positivity.

Figure 2 presents the imaging findings most strongly associated with the diagnosis of axSpA/ankylosing spondylitis or axPsA.

According to the graph, axial psoriatic arthritis (axPsA) is most likely to be diagnosed in the presence of osteolysis, joint ankylosis, extra articular bone proliferations, erosions, and multiple erosions on radiographs of the hands and/or feet. AxPsA is also characterized by cervical spine syndesmophytes, typically asymmetric, non bridging, and bulky, as well as spinal changes in the absence of sacroiliitis and the presence of radiographically definite sacroiliitis (RD SI). The presence of RD SI without inflammatory back pain is also typical.

In contrast, axial spondyloarthritis (axSpA) is most likely to be diagnosed when radiographically definite sacroiliitis and ankylosis of the sacroiliac joints are present.

To summarize the obtained data and identify the key distinguishing features, a multivariate analysis using classification tree modeling was performed (Figure 3).

According to the graph, the key features determining the differential diagnosis are the following PsA related characteristics:

- presence of psoriasis;
- joint pain severity ≥7 (BASDAI question no. 3);
- swollen joint count (SJC) >12;
- osteolysis on radiographs of the hands and/or feet.

Discussion. In the present study, a set of features for the differential diagnosis of axial psoriatic arthritis (axPsA) and axial spondyloarthritis (axSpA) was identified for the first time. Application of multivariate analysis using classification tree modeling demonstrated that the differential diagnosis is primarily based on the presence or absence of psoriasis in combination with peripheral manifestations and radiographic evidence of osteolysis.

It should be noted that in our cohort, psoriasis was present in all patients with axPsA, whereas in group 1 it was observed in only 3.7% of patients. These findings are supported by the study by T.S.H. Kwok et al. [22], who reported the presence of psoriasis in no more than 10% of patients with ankylosing spondylitis (AS). Our conclusion regarding the leading role of peripheral arthritis in the differential diagnosis of axPsA and axSpA is consistent with the results of the international ASAS PerSpA study [23], which demonstrated that peripheral arthritis was present in the vast majority of patients with PsA (90.8%), compared with only 36.0% of patients with axSpA [23].

Similar findings were obtained in a comparison of patients with axPsA and axSpA with concomitant psoriasis from the German RABBIT cohort [24]. Despite the presence of psoriasis in patients from both groups, peripheral manifestations were significantly more frequent in axPsA.

Notably, in the present study, one of the key differential diagnostic features distinguishing axPsA from axSpA was osteolysis of peripheral joints, rather than extra articular bone proliferations (a feature included in the CASPAR criteria). Indeed, osteolysis is considered a hallmark of PsA. According to the literature, osteolysis (as a manifestation of arthritis mutilans) is associated with axial involvement, specifically with radiographically definite sacroiliitis [25], as well as with the asymmetric syndesmophytes characteristic of axPsA [26].

Our findings are consistent with the results of previous studies [27, 28], which demonstrated that peripheral manifestations are more pronounced in axPsA, whereas axial involvement predominates

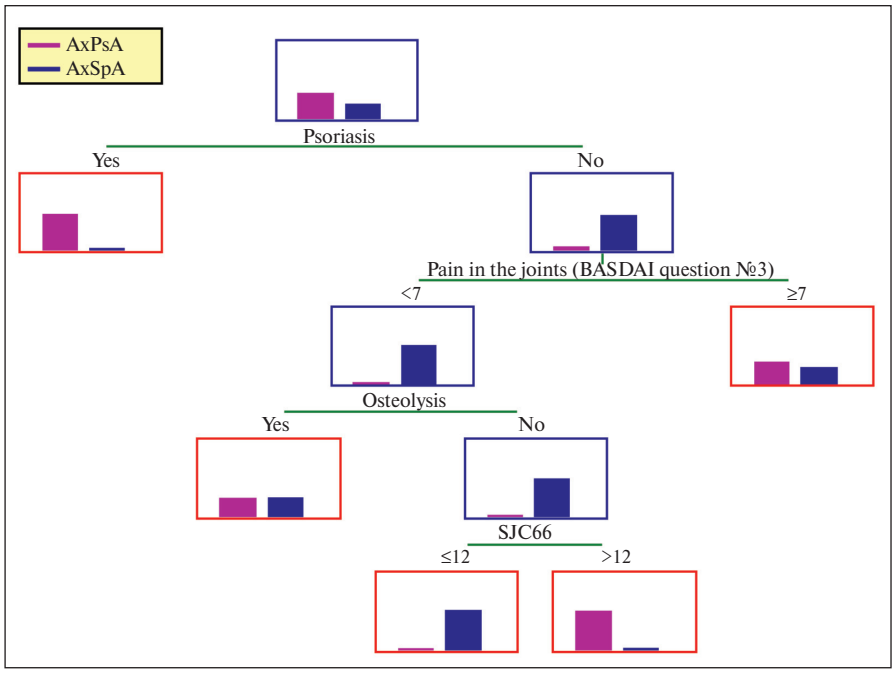

Fig. 3. *Classification trees illustrating the main differential diagnostic differences between axPsA and axSpA. BASDAI – Bath Ankylosing Spondylitis Disease Activity Index*

in axSpA. A diagnosis of axPsA is most likely in patients presenting with polyarthritis with a tender joint count (TJC) >5 and a swollen joint count (SJC) >3, dactylitis, radiographically detected joint destruction of the hands and feet (erosions, multiple erosions, osteolysis), and extra articular bone proliferations. Particularly noteworthy is that in our study, peripheral manifestations played a key differential diagnostic role even in patients with imaging confirmed axial involvement.

Statistical analysis identified the principal features that allow axSpA/ankylosing spondylitis (AS) to be diagnosed with the highest probability. Patients with axSpA/AS are younger and significantly more likely to exhibit HLA B27 positivity, inflammatory back pain, alternating buttock pain, isolated axial involvement without peripheral arthritis, and heel enthesitis. These findings are largely consistent with data reported by other authors [24] and with our previous studies [19, 29].

Extra skeletal manifestations such as uveitis and inflammatory bowel disease (IBD) are more characteristic of axSpA, which is also supported by other reports [30, 31]. We further demonstrated that a family history of spondyloarthritis and concomitant osteoporosis are more common in axSpA, whereas concomitant fibromyalgia is more frequently observed in axPsA.

Although classification tree modeling did not demonstrate significant discriminative value of radiographic features of axial skeletal involvement, we believe that all patients with psoriatic arthritis (PsA) should undergo conventional radiography of the pelvis, cervical spine, and thoracolumbar spine, including the two lower thoracic vertebrae, and—if radiographic markers of sacroiliitis are absent—MRI of the sacroiliac joints (SIJs) [14]. Imaging is essential for the timely diagnosis of axial involvement, as it is well known that 25–50% of patients may not experience back pain (so called silent sacroiliitis) [13].

As demonstrated in the present study, based on radiographic assessment of the axial skeleton, the highest likelihood of diagnosing axSpA/ankylosing spondylitis (AS) is associated with the presence of radiographically definite sacroiliitis and ankylosis of the SIJs, which is consistent with the findings of several studies [30, 32]. In contrast, a diagnosis of axial psoriatic arthritis (axPsA) is most likely in cases of radiographically definite sacroiliitis in the absence of inflammatory back pain, as well as in patients with spinal involvement without sacroiliitis, which fundamentally distinguishes axPsA from AS [12, 13]. Notably, spinal syndesmophytes in the presence of intact SIJs were identified exclusively in the axPsA group.

Thus, the presence of sacroiliitis and its severity play a crucial role in the differential diagnosis between axPsA and axSpA/AS. In addition, the present study confirmed data from previous reports [19, 29, 33] indicating differences in localization and morphological characteristics of syndesmophytes between axSpA/AS and axPsA. AxPsA is more commonly characterized by cervical spine syndesmophytes, as well as asymmetric, non bridging, and bulky (so called non marginal) syndesmophytes.

Differences in the morphological features of syndesmophytes in AS and axPsA are related to distinct pathophysiological mechanisms of new bone formation: osteitis (bone inflammation) underlies new bone formation in AS, whereas in axPsA it is primarily driven by ligamentitis (inflammation of ligamentous soft tissues) [34]. As previously demonstrated [35], the development of osteitis, in turn, is associated with HLA B27 positivity, which determines the distinct patterns of SIJ and spinal involvement in axPsA and axSpA.

In HLA B27–positive patients with axSpA/AS, new bone formation occurs at sites of prior osteitis, resulting in more pronounced radiographic sacroiliitis and the development of thin ("marginal"), symmetric, bridging syndesmophytes [34], representing ossification of the outer layers of the annulus fibrosus of the intervertebral disc. In contrast, in axPsA, ossification of inflamed ligaments located outside the disc leads to the formation of bulky, asymmetric, non marginal syndesmophytes [34].

According to our data [19], HLA B27 positivity is three times less frequent in axPsA than in axSpA/AS, which likely explains the rarer occurrence of radiographically definite sacroiliitis and "classic" syndesmophytes in axPsA.

Early diagnosis of axial skeletal involvement in psoriatic arthritis (PsA) is essential, as current concepts recognize axial involvement as an independent factor influencing therapeutic decision making. According to international and Russian clinical guidelines, patients with axial psoriatic arthritis (axPsA) are initially treated with nonsteroidal anti inflammatory drugs (NSAIDs); in cases of insufficient response, biologic disease modifying antirheumatic drugs (bDMARDs) are prescribed—primarily interleukin 17 inhibitors (IL 17i), followed by tumor necrosis factor α (TNF α) inhibitors, and, after risk assessment, Janus kinase (JAK) inhibitors [16].

Recently, the literature has widely discussed the results of post hoc analyses of randomized controlled trials [5, 36] demonstrating that patients with psoriatic spondylitis may respond to

therapy with IL 23 inhibitors (IL 23i) and IL 12/23 inhibitors, which have been shown to be ineffective in ankylosing spondylitis (AS) [7]. These findings are attributed to differences in the immunopathogenetic mechanisms underlying axSpA/AS and axPsA [37].

Interleukin 23 (IL 23) is a key mediator of the inflammatory cascade and, through activation of the IL 23/IL 17 axis, regulates the production of IL 17A [37]. It has been hypothesized that in the pathogenesis of axSpA/AS, IL 23–independent activation of Th17 cells predominates, leading to subsequent expression of IL 17A [37]. It is possible that IL 23–independent IL 17 production occurs at the spinal entheses, whereas in peripheral enthesitis, IL 17 expression is largely IL 23–dependent [38].

The results of the STAR randomized controlled trial (RCT) are anticipated and are expected to address many questions regarding the use of interleukin 23 inhibitors (IL 23i) in axial psoriatic arthritis (axPsA) [39]. In this study, a central expert review of magnetic resonance imaging (MRI) findings will be performed to assess changes in active sacroiliitis and spondylitis during guselkumab therapy.

Conclusion. Thus, the present study made it possible to identify a set of clinical and imaging related features characteristic of axial psoriatic arthritis (axPsA) for its differential diagnosis from axial spondyloarthritis/ankylosing spondylitis (axSpA/AS) in routine clinical practice. Notably, classification tree modeling did not demonstrate the discriminatory significance of any individual imaging feature of axial involvement.

It is likely that the identified set of differential diagnostic criteria may be used as a supplement to our previously developed diagnostic algorithm for axial involvement in PsA [14]. The establishment of a dedicated set of diagnostic criteria may facilitate early differential diagnosis of axSpA and axPsA and the timely initiation of targeted therapy, ultimately leading to a more favorable disease course.

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