LECTURE

Progression of axial spondyloarthritis

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The spectrum of bone lesions in axial spondyloarthritis is of great interest. With inflammation and mechanical influence concurrence in the background, both tissue gain and tissue loss in a particular bone area can occur simultaneously. Moreover, if vertebral bone mass loss, perhaps, can be easily explained by chronic systemic inflammation, the reason of its gain, observed in axial spondyloarthritis remains a mystery. It is unclear whether it is a consequence of enhanced recovery processes after injury, adaptation to altered mechanical stress, response to inflammatory cells activation or cytokines, produced by them, or changes in Wnt signaling pathways (for example). Whether these factors act individually or collectively is also unclear.

Key words: *axial spondyloarthritis; ankylosing spondylitis; biomarkers; progression; bone formation, bone gain.*
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The term «spondyloarthritis» (axSpA) combines non-radiological axSpA (nr-axSpA) and ankylosing spondylitis (AS), which is more and more often called X-ray axSpA. The main difference between these axSpa phenotypes is the presence or absence of radiographic changes in the sacroiliac joints or the spine. A variety of bone lesions in axSPA is characterized by competing processes that simultaneously occur in one area of the bone either with a loss or increase in its mass, or with activation of metabolism [1]. At the same time, if the loss of bone mass of the vertebrae can be explained by chronic systemic inflammation, then the cause of pathological bone formation raises questions: is it a consequence of excessive recovery after injury, adaptation to altered mechanical stress, reaction to the activation of cells involved in inflammation or cytokines produced by them, changes intracellular signaling pathways, and do these factors act separately or together?

Currently, it is believed that the progression of axSpA is associated primarily with a neoplasm of bone tissue (NOBT), manifested by the growth of enthesophytes, syndesmophytes and / or ankylosis of the joints.

Clinical features and instrumental signs of axSpA progression

Clinical signs

The development of bone proliferation in the axial skeleton is clinically manifested by an increasing limitation of the mobility of the spine. To identify and objectify this feature, special indices are used – the Bath Ankylosing Spondylitis Functional Index (BASFI) or the Bath Ankylosing Spondylitis Metrology Index (BASMI) [2]. In addition, the tests of Kushelevsky, Ott, Thomayer, etc., can additionally be used, although they do not belong to the methods of physical examination of patients recommended by ASAS (Assessment of Spondylo Arthritis international Society). With the growth of syndesmophytes or ankylosis of the joints of the spine, the restriction of mobility gradually increases. In severe cases, in the late stages of AS, a total ankylosis of the spine is formed, which radiographically looks like a "bamboo stick", which leads to complete immobility of this section of the axial skeleton [3].

Instrumental signs

Among the instrumental methods that allow observing the progression of axSPA, the main place is occupied by radiography. To assess structural damage, a number of scoring systems have been developed, among which the most commonly used is the modified Stoke Ankylosing Spinal Score (mSASSS) [4], designed to analyze changes in the anterior cervical regions (C_{II}–T_I) and lumbar (T_{XII}–S_I) vertebrae. The main disadvantage of this method is the lack of an assessment of the thoracic spine, in which the processes of syndesmophyte formation often develop in the first place. An increase in mSASSS by 2 units in 2 years indicates the progression of the disease and the appearance of syndesmophytes [5]; during this time, they first appear in almost 30% of patients with AS, and in about the same number of cases, an increase in already existing syndesmophytes is noted.

In the early stages of the disease, progression is assessed by the dynamics of the X-ray stage of sacroiliitis (SI), since in this phase of the disease there are no syndesmophytes and other bone-proliferative lesions of the vertebrae that could be analyzed using mSASSS. To determine the radiological stages of the defeat of the sacroiliac joints (SIJ), the Kellgren–Lowrence classification [6], created more than half a century ago, is used. However, due to the poorly informative description of SI stages in this classification, they are often misinterpreted [7, 8]. To eliminate this disadvantage, extended explanations to the Kellgren–Lowrence classification were recently published, simplifying the diagnosis of SI in axSpA [9]. In recent years, to analyze the dynamics of X-ray changes in the SIJ, methods have been proposed for determining the total SI count [10] and the rate of its X-ray progression [11]. The use of these techniques showed that the progression of SI within 2 years is observed in almost 40% of patients with early axSpA.

The main limitation of conventional X-ray imaging of syndesmophytes is that it cannot estimate their volume, which is necessary for more accurate measurement. Although syndesmophytes of different sizes can be assessed on conventional radiographs, their minimum detectable parameters are unknown. Also, the criteria for the minimum height required to classify the obtained X-ray projection as syndesmophyte have not been

developed. In addition, their identification at the level of the lumbar spine is often difficult due to the accumulation of intestinal gases [12].

To overcome this drawback, when monitoring patients with axSpA, computed tomography (CT) is increasingly being introduced, which allows not only visualizing syndesmophytes, but also accurately measuring their sizes in three-dimensional space and obtaining an accurate quantitative characteristic for subsequent analysis using an automatic tomogram evaluation system [12]. In the near future, it seems that there will be studies that will determine the growth rate of syndesmophytes, both in length and in volume, in patients with various risk factors for disease progression. Already now, according to CT data, it has been shown in dynamics that not all syndesmophytes in AS grow simultaneously and continuously, and the growth rates over 24 months differ both in syndesmophytes in the same intervertebral disc spaces and in syndesmophytes in the same patient. [13].

Another method that has recently been introduced into clinical practice is spectral (dual-energy) CT, which measures the relative concentration of water and calcium in bone tissue. Using sequential high and low energy scans (140 and 80 kV) using a single X-ray tube, high-performance detector and powerful post-processing imaging, this method not only detects bone erosion and sclerosis, but also quantitatively measures bone marrow edema, and, according to available data , not worse than magnetic resonance imaging (MRI) [14, 15], therefore it can be used in patients for whom MRI is contraindicated [16].

Recently, with axSPA, the possibilities of positron emission tomography (PET) have been actively studied. Thus, it has been shown that in patients with SpA, abnormal uptake of 18F-NaF (sodium salt of the radioactive isotope fluorine with atomic number 9 and mass number 18) in the SIJ during PET is detected more often (87.0%) than inflammatory (43.5%) and chronic SI (65.2%) on MRI. Moreover, the assessment of SI activity using PET correlates well with inflammation in the SIJ, determined by MRI, but does not reveal a connection with structural lesions of the joint [17].

Currently, MRI is becoming one of the main imaging methods, which, along with standard radiography, is widely used for the diagnosis and monitoring of axSpA. MRI data are among the key features that form the basis of the ASAS classification criteria [18] and the domestic version of the modified New York AS criteria [19].

It was previously shown that syndesmophytes – the most important marker of AS progression – develop in the vertebrae at the site of the previous osteitis diagnosed by MRI [20]. However, later it was found that they are also often found in places where inflammation was not previously visualized [21]. Based on this, it can be assumed that if MRI was performed more often, then in these areas, signs of osteitis might be detected, or the processes of inflammation and bone formation in some patients proceed independently of each other. In addition, bone hyperproliferation is likely to be part of a defense mechanism aimed at stabilizing the joint [22]. It is believed that the process of osteoproliferation can be triggered by several molecules, such as bone morphogenetic proteins, proteins of the Wnt signaling pathway and fibroblast growth factors, and inhibited by sclerostin, DKK1 (Dickkopf-related protein 1), and Noggin [23].

Later, it was shown that over time, osteitis detected by MRI is replaced by adipose metaplasia of bone tissue, in the place of which NOBT develops later [24]. However, not all MR-inflammatory bone lesions progress to syndesmophytes or ankylosis. The likelihood of NOBT increases in the presence of sclerosis or erosions with residual signs of inflammation [25].

It should be noted that MRI does not always show the presence of inflammation, for example, in the SIJ. Thus, when comparing the results of puncture biopsy (PB) and MRI of the SIJ in patients with early AS, it turned out that active SI was detected in 78 and 30% of cases, respectively. At the same time, all cases of MRI of active SI were confirmed by PB, and with MRI-negative SI, acute inflammation in the SIJ was determined in 70% of biopsies. Interestingly, dynamic follow-up for 5–10 years revealed progression of SI in almost 90% of patients with MR-active SI and in 53% of patients in whom inflammation was diagnosed based on LB [26]. It should be emphasized that inflammatory changes in SIJ biopsies are characterized by bone marrow inflammation, pannus formation, destruction of the subchondral bone plate, cartilage degeneration / erosion, synovitis and enthesitis [27] in different combinations depending on the stage of SI. The morphological data obtained suggested that SI begins with bone marrow inflammation, followed by pannus formation, destruction of the subchondral bone plate, and cartilage degeneration / erosion, resulting in fibrosis, sclerosis, and ankylosis of the SIJ [28]. At the same time, synovitis and enthesitis are not the earliest changes in SI. In the initial stage of ankylosis, cartilaginous adhesions predominate, which are formed when the adjacent tissues of the joint are destroyed due to osteitis and expanding pannus. Subsequently, both the original and the reparative cartilage tissue is replaced by bone. At the same time, a large number of CD20 + B-cell infiltrates are found in the inflamed areas of the SIJ, which are simultaneously determined in fibrous tissue resembling pannus, which indicates the participation of B-cells in inflammation in axSpA [29].

Thus, the study of the mechanisms of axSpA progression and the factors affecting its rate remains an urgent task. Available data indicate that a higher activity is associated with major structural damage to the spine. [30] It is well known that clinical predictors of faster progression are male sex, high serum CRP levels and pre-existing syndesmophytes [31], as well as obesity [32]. Concomitant vertebral inflammation and post-inflammatory changes detected by MRI, in certain situations, can be considered as predictors of syndesmophyte growth, but in most cases they do not have MRI precursors. Treatment measures play an important role in curbing the progression.

Effect of axSPA therapy on NOBT

A. Wanders et al. [33] found for the first time that continuous use of celecoxib for 2 years slows the progression of AS. Subsequent post hoc analysis showed that this effect is more pronounced in patients with increased levels of acute phase markers of inflammation or high / very high disease activity according to the ASDAS index. (Ankylosing Spondylitis Disease Activity Score) [34]. Further, when assessing the effectiveness of diclofenac for 2 years, the inhibition of the progression of AS could not be confirmed [35]. Whereas in another two-year observational study, it was shown that in patients with AS with a high index of nonsteroidal anti-inflammatory drugs (NSAIDs) intake, there is a decrease in structural damage to the spine compared with patients in whom this index was low. This protective effect was observed almost exclusively in patients who initially had syndesmophytes and elevated CRP levels [36]. Recently, based on the results of our own work, we suggested that in patients with

early axSpA, continuous use of NSAIDs can reduce X-ray progression not only in the spine, but also in the SIJ [37].

Another group of drugs that affect the progression of axSpA are genetically engineered biological drugs (GIBD). The first studies of tumor necrosis factor α (TNF-α) inhibitors were conducted by comparing data from short-term clinical trials with the results of a study of historical cohorts of patients with AS who did not receive TNF-α. The duration of these studies was insufficient to prove the protective effect of BAs on X-ray progression [38]. Later, with the use of modern assessment methods, a significant decrease in the structural progression of the disease was demonstrated with early and continuous use of TNF-α, especially if the duration of treatment exceeded 4 years [39, 40]. Subsequent analysis also showed that the use of TNF-α for 4–8 years significantly slows down the progression of AS [41]. Later, the statement that long-term therapy with TNF-α inhibits pathological bone tissue proliferation in axSPA was confirmed in numerous studies [42–45]. In addition, when assessing the effect of infliximab on the state of bone tissue, a significant improvement in its metabolism was found [46], which is consistent with previously obtained and current data on the positive effect of TNF-α on bone mineral density [47, 48].

The role of biomerkers of inflammation and bone metabolism in NOBT in axSpA

Genetic heterogeneity of axSpA and NOBT

Genetic factors play an important role in the predisposition to SpA, as confirmed in studies of general genome associations (Genome-Wide Association Studies, GWAS). One of the main genetic factors for AS is HLA-B27, which is found in about 90% of patients. However, the contribution of HLA-B27 to the inheritance of this disease is approximately 20%, another 7.4% is accounted for by 113 identified to date single nucleotide polymorphisms (SNPs) associated with AS [49]. It should be noted that no direct effect of HLA-B27 on chondrogenesis or osteogenesis has been obtained in the model of collagen-induced arthritis (collagen antibody-induced arthritis, CAIA), ie, its direct role in pathological bone formation in axSpA is unlikely [50].

GWAS made it possible to identify common genes, including the interleukin (IL) 23 receptor, IL12B, STAT3, and CARD9, which are associated not only with SpA, but also with psoriasis and inflammatory bowel diseases [51, 52]. At the same time, ERAP 1 and ERAP2 (endoplasmic reticulum aminopeptidase) are endogenous peptides for HLA-mediated presentation in the immune system. SNPs of these genes are strongly associated with AS [53]. However, these genetic determinants are primarily associated with inflammation and do not directly affect bone formation in this disease.

Bone metabolism markers and NOBT in axSpA

New bone formation is a delicate balance between activation and inhibition of the Wnt signaling pathway associated with secreted frizzled related protein (sFRP1), DKK1, sclerostin and the participation of factors such as BMP (Bone morphogenetic proteins) and others [54]. As for DKK1, in AS, its general or functional level was measured [55, 56]. The results of the studies revealed a dysfunction of DKK1 in this disease [57]. It was also shown that the level of DKK1 positively correlates with markers of systemic inflammation (ESR and CRP), as well as with the level of sclerostin [58]. In addition, high DKK1 levels were independently associated with the absence of syndesmophytes and, as a rule, with low mSASSS. So, according to E. Klingberg et al. [56], AS patients with mSASSS equal to 0 had a higher level of DKK1 compared with those with mSASSS> 20. In turn, in the GESPIC cohort, a high level of DKK1 predicted the absence of syndesmophyte formation [55]. All these data indicate that the Wnt signaling pathway can support the formation of syndesmophytes in AS. However, in the mouse model of AS, sclerostin (an endogenous inhibitor of the canonical Wnt/β-catenin signaling pathway) could not prevent the development of peripheral or axial manifestations of the disease, as well as affect its severity and bone density [59]. Currently, there are no data to confirm the role of signaling molecules of the Wnt family in the pathogenesis of NOBT in patients with SpA. Thus, although the level of sclerostin has been proposed as a biomarker for the progression of SpA, many white spots remain in this area, in particular, impaired secretion of sclerostin and DKK1 may be a consequence, not a cause, of changes in bone tissue in this disease. Apparently, the expression of osteoinductive proteins Wnt, dependent on the intensity of inflammation, is a key link between inflammation and ectopic new bone formation in AS. Activation of the canonical Wnt/β-catenin pathway and the noncanonical Wnt/PKCδ pathway is required for inflammation-induced new bone formation both in experiments in mouse models and in patient tissues [60]. It has been shown experimentally that constitutionally low TNFα expression, rather than a short-term increase or its high level, induces persistent Wnt expression through the NF-κB and JNK pathways (c-Jun N-terminal kinases) with the subsequent formation of new bone. The JNK signaling pathway regulates a wide range of cellular processes, including cell proliferation, differentiation, survival, apoptosis, and inflammation. Dysregulation of this pathway is associated with the development of not only oncological diseases, but also many immune disorders [61].

Several years ago, it was shown that BMP6 (Bone Morphogenetic Protein 6) polymorphisms correlated with the severity of the radiological progression of AS. Two SNPs in BMP6 (rs270378 and rs1235192) have been associated with an increased risk of syndesmophyte formation, presumably independently of each other [62]. In turn, it is well known that BMPs are growth and differentiation factors belonging to the TGFβ (Transforming growth factor β) superfamily. On the periosteal surface, BMPs increase the expression of Id genes in the surrounding muscles, which leads to endochondral bone formation, spreading from the bone surface into the medullary canal. They also stimulate the differentiation of periosteal progenitor cells into osteoblasts [63].

In addition, a recently published meta-analysis showed that the serum BMP2 level in AS patients is higher than in healthy controls, while the level of sclerostin did not differ significantly [64]. It was also found that serum BMP7 and BMP7 / DKK1 ratio statistically significantly correlate with the severity of CI, radiographic indicators of progression and duration of AS, and BMP2, BMP4, and BMP6 correlate with BASRI (Bath Ankylosing Spondylitis Radiology Index) and disease duration [65].

In recent years, interesting data have been obtained on the role of adipokines in the pathogenesis of AS. Serum levels of resistin and visfatin have been shown to be elevated in this disease. In this case, the level of resistin was associated primarily with markers of inflammation, and an increased level of visfatin was an inflammation-independent predictor of X-ray progression of AS

[66]. Further studies found a significant relationship between structural changes in the spine and leptin levels, as well as high molecular weight forms of adiponectin. The baseline levels of these adipokines in the blood serum were lower in patients with AS, who showed structural progression in the spine after 2 years of follow-up. This association was especially pronounced in men, in whom the serum levels of these adipokines were lower than in women. These results explain why women are less likely to experience structural damage to the spine than men [67]. According to South Korean authors, the level of resistin, like leptin, correlated with radiological progression of the disease, and not with inflammation [68].

In recent decades, a number of biomarkers associated with X-ray changes in the spine in axSpA have been identified: CRP [69], matrix metalloproteinase 3 [70], vascular endothelial growth factor [71], calprotectin [72] and visfatin [73], however, at present For the time being, only CRP is widely used in clinical practice. It has been shown that an increased level of CRP statistically significantly predicts X-ray progression of AS in patients receiving NSAIDs and synthetic basic anti-inflammatory drugs [69, 74], as well as TNFα [75, 76]. At the same time, a decrease in the level of CRP correlated with a decrease in inflammation in the vertebrae, revealed by MRI, and subsequently led to a slowdown in NOBT.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) may also play an important role in NOBT in SpA. In the blood and joints of patients with SpA, an increase in the number of GM-CSF-producing CD4 + and CD8 + lymphocytes, as well as expressing IL-17A + and GM-CSF + CD4 +, CD8 +, γδ T cells and NK cells was found [77]. Blocking GM-CSF in an experiment on a mouse model (SKG) AC led to the complete disappearance of bone lesions – erosions in the peripheral joints and additional bone formation in the periosteum [78].

It has recently been shown that circulating microRNAs (miRs) serve as a diagnostic tool for several human diseases, including AS. In patients with AS, compared with healthy donors, high levels of expression of miR-146a-5p, miR-125a-5p, miR-151a-3p, and miR-22-3p were found, as well as lower expression of miR-150-5p and miR- 451a. Bioinformatic analysis revealed that miRs target genes for inflammation and bone remodeling, which play a potential role in this pathology. Indeed, additional studies have identified the relationship between miRs and potential target proteins associated with the pathophysiology of AS. In addition, the expression of miR-146a-5p, miR-125a-5p, and miR-22-3p was increased in patients with active and inactive AS, while the expression of miR-125a-5p, miR-151a-3p, miR- 150-5p and miR-451a has been associated with the presence of syndesmophytes [79].

Currently, it has been suggested that NOBT in SpA is an overreaction of tissues to mechanical stress and inflammation. It is believed that osteocytes are the main mechanosensitive bone cells that are able to perceive and respond to mechanical stimuli, decreasing the release of sclerostin in response to mechanical stimuli acting on the bone, thereby promoting the activation of the osteogenic Wnt/β-catenin pathway in osteoblasts [80].

It has been shown that in CAIA mice, in the absence of mechanical stress, osteophytes are significantly less [81]. These results formally support the concept that mechanical stress leads to both enthesial inflammation and new bone formation in SpA.

It was previously found that in patients with AS, with a decrease in the expression of sclerostin, which is an important protein in the response to mechanical stress and encoded by the SOST gene, X-ray progression was enhanced, which emphasizes its role in suppressing bone formation [82]. It is also known that osteoblasts react to mechanical stress, which leads to an increase in bone formation. In addition, it has recently been established that cells obtained from the facet joints of patients with AS, in contrast to cells obtained after spinal trauma, have an increased osteogenic capacity [83]. Thus, a combination of decreased Wnt inhibition, changing mechanical stress, and an increased tendency to form osteoblasts may contribute to the formation of syndesmophytes in axSpA [84].

There is evidence that the IL17–IL23 axis is central to the pathogenesis of axSpA. Compared to healthy individuals (control), in patients with AS, a distortion of the T-helper cell profile towards Th17 cells is observed in the peripheral blood. IL17, released by TH17 and other cells, is highly pro-inflammatory. It was previously thought that IL17 primarily induces osteoclastogenesis [85], but recent studies have found that it has a direct stimulating effect on osteoblasts and their mesenchymal precursors [86, 87], regulating their activity and differentiation through the JAK2 / STAT3 signaling pathway [88]. In a model of transgenic rats with AS in vivo, it was shown that inhibition of IL-17A decreased inflammation and bone formation, which is additional evidence of the importance of this cytokine in bone metabolism [89].

If the influence of IL-17 on NOBT in SpA finds more and more confirmation, then the role of IL-23 in this process is being questioned. Although IL-23 induces the production of IL-17 and many mouse models of AS demonstrate a strong dependence on this cytokine, the results of clinical trials of IL-23 inhibitors have shown insufficient efficacy of these drugs, including in inhibiting the progression of the disease, which indicates a difference in the role of IL-23 in spinal and peripheral skeletal enthesis [90]. Consequently, the available evidence substantiates the importance of the IL17 – IL23 axis in the pathology of bone tissue in SpA, but at the same time suggests that its effect may differ in different parts of the skeleton.

Conclusion

Thus, in axSpA, osteoproliferation, in particular the formation of new bone in the area of enthesises, affects both the clinical picture and early disability and long-term outcomes. To solve the problem of NOBT, reliable prospective clinical studies are needed, which will contribute to the development of new therapies aimed at reducing pathological bone formation.

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Conflict of Interest Statement

The investigation has been conducted within scientific topic № R&D AAAA-A20-120041490010-4 «Development of methods for diagnostics and remote monitoring of damage to the axial skeleton in ankylosing spondylitis and psoriatic arthritis».

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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