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Extrasceletal Manifestations in Patients with Ankylosing Spondylitis

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Abstract

Extraskeletal manifestations (EM) are often observed in ankylosing spondylitis (AS). The available data on the association of EM with inflammatory activity and other clinical parameters of AS are contradictory.

The purpose of the study was to evaluate the association of EM with inflammatory activity and other manifestations of AS.

Patients and methods. At the Tashkent state clinic hospital examined 100 patients (89 men and 11 women) diagnosed with AS according to the New York criteria (1984). The median age of patients was 31.5 years, the age of onset of the disease was 19.5 years and its duration - 11.5 years. 97 (97%) patients identified HLA-B27. In addition to the standard clinical, laboratory and instrumental examination, 52 patients underwent transthoracic echocardiography, ultrasound diagnostics of the kidneys, colonoscopy, consultations of an ophthalmologist, dermatologist, nephrologist, gastroenterologist. Uveitis, heart damage (impaired conduction, changes in the aorta and valves), inflammatory bowel disease (IBD) and psoriasis were considered as EMs. 18 (18%) of 100 patients had uveitis, 21 (21%) had cardiac conduction disorders, 17 (17%) had psoriasis, 6 (6%) had IBD, 41 (41%) out of 100 - changes in the aorta and heart valves. The I group of patients with EM (n=35) and II group without EM (n=65) were compared according to the age of onset of AS, the presence of HLA-B27, arthritis of the peripheral joints, coxitis, enthesitis, syndesmophytes, fever, anemia, and the need for gene- engineering therapy, biological drugs (GIBD) and / or systemic glucocorticoids (GC), the value of the BASDAI, BASMI, BASFI, ASDAS indices, VASc scale and ESR.

Results. The groups with and without EM were comparable in terms of gender, age, duration of AS, and the presence of HLA-B27. There were no significant differences in the ESR, BASDAI, frequency of coxitis, enthesitis, syndesmophytes in the spine.

In the group with EM peripheral arthritis was significantly more common than in the group without EM – in 29 (82.8%) of 35 and in 42 (65,6%) of 65 patients, respectively ($p<0.0001$) ; fever - in 4 (11,4%) of 35 and 8 (12,3%) of 65 patients, respectively ($p<0.0001$), anemia- in 9 (25,7%) of 35 and 16 (24,6%) of 65 patients, respectively ($p<0.0001$); use of GIBP and/or systemic GCs -in 18 (51,4%) of 35 and 26 (40,0%) of 65 patients, respectively ($p<0.0001$).

1. Introduction

Ankylosing spondylitis (AS) is an inflammatory disease with an extremely heterogeneous phenotype, ranging from an isolated axial lesion to involvement along with spine, joints and enthesis also eyes, skin, internal organs. The frequent development of extraskeletal manifestations (EM) in AS is confirmed by the data of numerous studies and clinical observations [1–4].

However, despite the recognition by most rheumatologists of the importance of the problem of EM in AS, many unresolved questions remain regarding the definitions, classification, clinical and prognostic significance of EM: are EM associated with other manifestations of AS, including damage to the peripheral and hip joints, entheses, as well as parameters of inflammatory activity AS, structural progression, functional violations? Definitive answers to these questions so far no. Individual EPs, such as uveitis, are considered as "benign", with a rare development of complications and not skeletal lesion-dependent course [5, 6]. The same there is also an opinion regarding damage to the heart and aorta [7]. Comparison of damage to the aorta, heart valves, conduction disturbances with clinical characteristics of AS showed that they are associated with age, male sex, duration of the disease, its early onset [8]. The relationship between the pathology of the aorta and heart valves and other clinical manifestations of AS, as well as laboratory indicators of inflammation activity, has not been established. According to S.A. Roldan et al. [9], H. Przepiera-Bezak and et al. [10], the values of the BASDAI indices (Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index, Bathy functional index of ankylosing spondylitis), characterizing clinical activity, functional disorders and global assessment of the condition of patients with AS, as well as ESR and CRP did not differ

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between patients with and without aortic and/or valvular disease.

The purpose of the study was to assess the association of EP with inflammatory activity and other manifestations of AS.

2. Materials and Methods.

The study included 452 patients with a reliable diagnosis of AS, corresponding to the modified New York criteria (1984) [14]. All patients were observed at the Tashkent clinical hospital №3 in a hospital or on an outpatient basis, for at least 2 years. The patients included 82 men and 18 women. The median for the age of patients at the time of observation was 41.5 [24; 41] years, the age of onset of the disease was 19.5 [15; 23] years, disease duration - 11.5 [7; 18] years. 27 (27%) of patients, the disease debuted before the age of 16 years (juvenile onset). The axial form of AS (with an isolated lesion of the axial skeleton) was observed in 64 (64 %) patients, peripheral arthritis -in 36 (36 %), damage to the hip joint (coxitis) - in 48 (48.0%). HLA-B27 was detected in 93 (93%) patients. General features of patients are presented in table. 1.

Table 1.

Features	**Frequency**
Men/women,n	82/18
HLA-B27 +/-	93/7
Age, years, Me	41.5
Onset of disease, years, Me	19.5
Disease duration. years, Me	11.5
Debute up to 16 years, %	27
Axial form, n (%)	64
Peripheral arthritis, n (%)	36

All patients underwent a comprehensive examination, accepted in the rheumatology clinic, with a detailed assessment of AS manifestations. The family history was studied: the presence of psoriasis in relatives, inflammation of the eyes, intestines, heart defects. A psoriatic lesion of the skin and nails was recorded, auscultatory signs of changes in the heart (bradycardia, murmurs). At objective study of the musculoskeletal system, peripheral joints, hip joints and entheses, mobility of the spine using the BASMI index (Bath Ankylosing Spondylitis Metrology Index, Bath metrological index of ankylosing spondylitis) [15]. BASDAI and ASDAS indices were used for the inflammatory activity of AS [15]. All patients underwent laboratory tests: clinical analysis of blood and urine, CRP, ESR.

In all patients, the histocompatibility antigen HLA-B27 was determined in the Laboratory of Immunology and Human Genomics Institute using a standard micro lymphocytotoxic test using specific anti-HLA sera (CJSC Gisans). In all cases, standard instrumental examinations were performed: X-ray of the pelvis with an assessment of the sacroiliac (SIJ) and hip joints, radiography of the cervical, thoracic and lumbar regions spine, electrocardiography (ECG) in 12 leads. When analyzing the ECG, the presence and severity of conduction disorders. 72 patients underwent transthoracic echocardiography (EchoCG) on ultrasound devices of the GE Vivid 7 system (USA), ESAOTE TWICE (Italy). When analyzing echocardiographic changes, we analyzed the following signs: thickening of the walls of the aorta (thickness

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posterior wall of the aorta at a distance of 2-3 cm from the aortic valve >3 mm), dilatation of the aortic root (>3.7 cm), thickening of the leaflets of the heart valves (>3 mm), the presence and severity of valvular regurgitation, the presence of subaortic ridge-like thickening (subaortic bump) [16, 17].

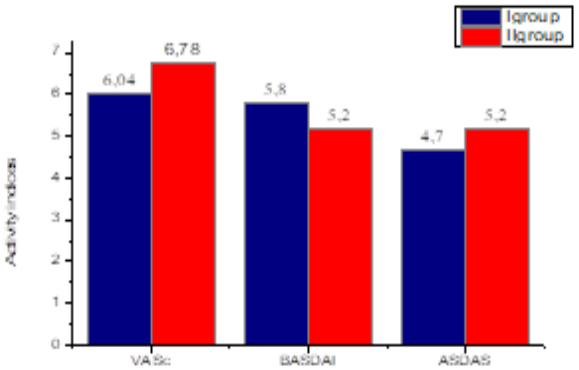
Careful assessment of data from a comprehensive examination of patients with EM made it possible to exclude lesions of various organs and systems that could be caused by various factors, including infectious, age-related, comorbidities, or drug therapy. Thus, inflammatory processes associated with the underlying disease. Evaluation of the results of clinical, laboratory, instrumental research in each patient, taking into account literature data and previous clinical observations, made it possible to identify the following symptom complexes, which were regarded as EP and subjected to further analysis: uveitis, damage to the aorta and heart valves, impaired conduction, IBD, psoriasis.

The EM structure was dominated by uveitis and heart damage (changes in the aorta and heart valves, conduction disturbances), which were analyzed in more detail; the proportion of other EMs (psoriasis, IBD, nephritis) was less than 8%. To assess the relationship of EM with other clinical manifestations of AS were compared two groups of patients - with EM (n=35) and without EM (n=65), in which the following indicators were compared: age of onset of AS, presence of HLA-B27, arthritis of the peripheral joints, arthritis of the hip joints, enthesitis, syndesmophytes, index values BASDAI, ASDAS, BASFI, BASMI, ESR. In addition, in these two groups, we compared the number of patients who had fever, anemia due to the underlying disease during the course of the disease, and were also treated with systemic glucocorticoids (GCs) or genetically engineered biological drugs (GIBP).

Statistical data processing was carried out using computer programs Origin Pro 7 and Microsoft Office Excel 2007. Statistical analysis compared the studied indicators in different groups. To describe quantitative variables, we used the methods of descriptive statistics with the calculation of averages values and standard deviations. Data that does not have normal distribution, expressed as a median (Me). Significance of differences was determined using two tailed Fisher's exact test. Differences were considered significant at $p<0.05$.

Groups were comparable in terms of sex, age of onset of the disease at the time of observation, and duration of AS. Frequency HLA-B27 detection also did not differ significantly in both groups. Comparison of clinical parameters of AS, a significantly more frequent presence of peripheral arthritis was found in patients with EM. Number of patients with coxitis, enthesitis, syndesmophytes in the cervical and lumbar regions spine did not differ significantly between the two groups.

Although the magnitude of the ESR and the BASDAI index are reliable no differences were found between the groups, in patients with EM.



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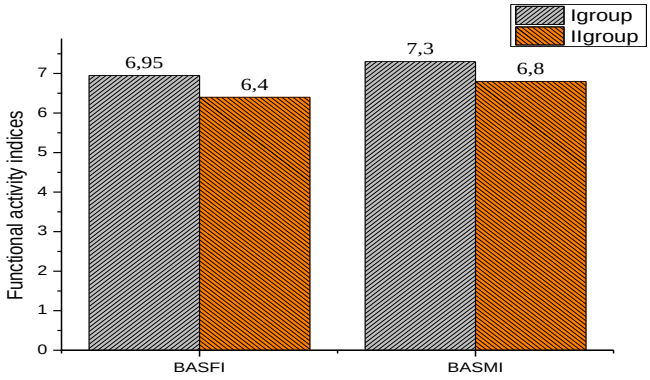

Figure 1. Comparison analyses of activity and functional indices in I and II groups

Significantly more frequently observed signs characterizing high inflammatory activity: fever, anemia, and also the appointment of anti-inflammatory therapy with the use of GIBP or systemic GCs. In the I group, 10 (28,5%) of 53 patients received due to high inflammatory activity, insufficient effectiveness of standard anti-inflammatory therapy, and 8 (22,8%) - systemic GCs in the form of pulse therapy or long-term oral administration.

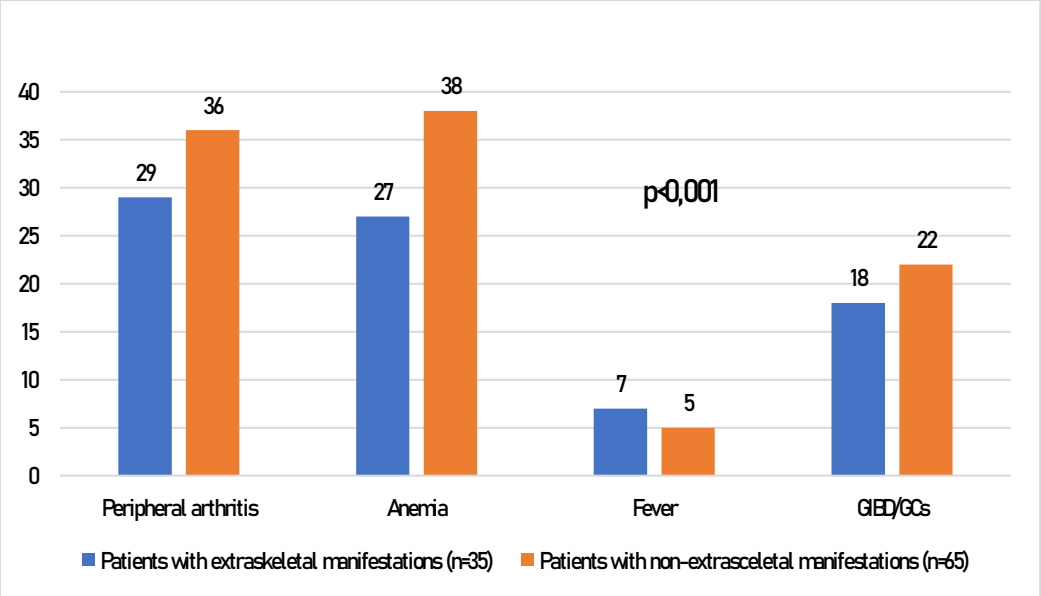

Figure 2. Comparison analyses of patients with peripheral arthritis, anemia, fever and GIBD/GC sufficiency in both groups

Clinical case.

Patient A., 39 years, was admitted to the clinic with complaints of inflammatory pain in lumbar spine, pain and swelling in the left knee, ankle joints. From the anamnesis it is known that night back pain and morning stiffness has been a concern for about 15 years. The patient periodically took non-steroidal anti-inflammatory drugs (NSAIDs). Over the past 5 years - uveitis (iridocyclitis), recurrent on average 1 time per year, with progressive eye injury is mentioned. 3 months ago, after a nasopharyngeal infection, pain and swelling appeared in the left knee, ankle joints, increased pain in the spine and an increase in temperature to 38°C. Taking NSAIDs in full therapeutic doses did not give a significant effect, intra-articular injections of AS caused a short-term improvement.

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Physical examination of the internal organs revealed no pathological changes. The BASDAI index was 8.0. Blood test: Hb 92 g/l, ESR 62 mm/h, CRP 125.0 mg/l. EchoCG: compaction of the aortic valve leaflets, marginal thickening of the mitral valve leaflets (Fig. 2).

Figure 2. Marginal thickening of the mitral valve leaflets

X-ray of the pelvis: bilateral sacroiliitis stage III, narrowing of the gaps of the hip joints (Fig. 3).

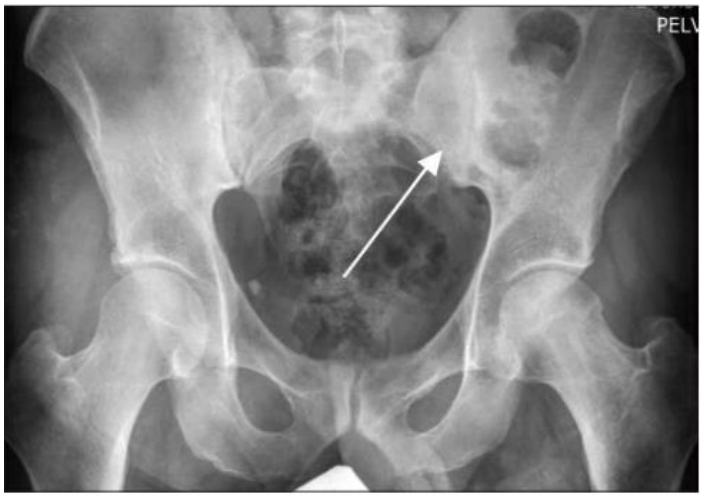

Figure 3. Sacroiliitis stage III.

Magnetic resonance imaging (MRI) of the SIJ and lumbar spine: signs of chronic sacroiliitis and active inflammation in the left SIJ, chronic spondylitis. Other tests, including biochemical blood tests, urinalysis, bacteriological tests synovial fluid, esophagogastroduodenoscopy, colonoscopy, ultrasound of the abdominal organs, kidneys, thyroid glands, clinically significant changes were not revealed. In this patient, along with active spondylitis peripheral joint damage, EP (recurrent uveitis, hardening of the heart valves) were observed. The disease proceeded with high clinical and laboratory activity, fever, anemia, and required the use of systemic GCs.

3. Discussion.

The question of the correlation between the course of CAP and inflammation of the musculoskeletal system in AS remains debatable. Although many publications express opinion about the absence of a relationship

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between the course of AS and the activity of spondylitis and arthritis, our data show that a number of AS activity and severity parameters correlate with EP.

An analysis of 100 patients with AS demonstrated that most of them (60%) during the observation revealed high indicators of laboratory activity (ESR, CRP), half (49.5%) have a high level of BASDAI. Although the level of BASDAI and ESR did not differ significantly in patients with and without EM. In patients with EM, arthritis of the peripheral joints was significantly more common, which is evidence of a generalization of the inflammatory process with extraaxial defeats.

The need for active anti-inflammatory treatment is also an indicator of the severity of the disease. From 35 patients with EM 18 (51.4%) required GEBD therapy or systemic GCs, of which 16 (45.7%) received both GCs and GIBP, which was significantly higher than in the group without EM. At the same time, exacerbations of uveitis or IBD did not always coincide in time with an exacerbation of spondylitis or arthritis. As for active aortitis or valvulitis, they are difficult to verify, so it is difficult to judge whether they with exacerbation of spondylitis/arthritis, in most cases it is impossible.

Findings. The inflammatory process that develops with AS, it covers, along with the musculoskeletal system, other structures (eyes, heart, skin, intestines), the defeat of which can manifest itself at different times, and a combination of these manifestations is often observed. EMs are associated with inflammatory activity and disease severity. Thus, EMs in patients with AS are associated with peripheral arthritis and indicators of inflammatory activity.

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