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THE BURDEN OF SYSTEMIC INFLAMMATION AND MULTIORGAN INVOLVEMENT IN ANKYLOSING SPONDYLITIS: CLINICAL PATTERNS AND THERAPEUTIC PERSPECTIVES

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Introduction

Ankylosing spondylitis (AS) is a prototypical form of axial spondyloarthritis characterized by chronic inflammation of the sacroiliac joints and spine, progressive structural damage, and functional impairment. Historically regarded as a disease confined to the axial skeleton, AS is now understood as a systemic inflammatory disorder with diverse clinical expressions.

The pathogenesis of AS involves complex interactions between genetic predisposition, immune dysregulation, and environmental triggers. The strongest genetic association is linked to the HLA-B27 antigen, which plays a critical role in antigen presentation and immune activation. Although HLA-B27 positivity is present in the majority of AS patients, its exact pathogenic contribution remains incompletely elucidated.

Beyond axial skeletal inflammation, AS frequently presents with multiorgan manifestations. These include:

- Acute anterior uveitis
- Peripheral arthritis
- Enthesitis
- Inflammatory bowel disease
- Cardiac conduction abnormalities and valvular disease
- Pulmonary fibrosis
- Osteoporosis and hematologic disturbances

Such manifestations substantially modify disease burden and may precede or accompany axial symptoms. Importantly, systemic involvement often reflects heightened inflammatory activity and may correlate with more aggressive disease phenotypes.

Despite advances in biologic therapies targeting TNF-α and IL-17 pathways, the relationship between systemic inflammatory burden and organ-specific involvement remains an area of active investigation. Understanding this relationship is essential for personalized therapeutic strategies and improved long-term outcomes.

This study aims to evaluate the association between systemic inflammatory activity and multiorgan involvement in AS, focusing on clinical severity, functional impairment, laboratory markers, structural progression, and treatment patterns.

Materials and Methods

Study Design and Population

A cross-sectional observational study was conducted involving 452 patients diagnosed with AS according to the modified New York criteria. Patients were recruited from a tertiary rheumatology center and underwent standardized clinical evaluation.

Inclusion criteria:

- Age ≥18 years
- Definite AS based on radiographic sacroiliitis
- Complete clinical and laboratory records

Exclusion criteria:

- Overlapping autoimmune disorders
- Active infection
- Malignancy

Among the total cohort, 100 patients were selected for detailed comparative analysis:

- Group A: 35 patients with documented multiorgan/systemic manifestations
- Group B: 65 patients without documented systemic involvement

The median age of the analyzed population was 41.5 years, with disease onset at a median age of 19.5 years and median disease duration of 11.5 years. Male predominance was observed, consistent with known epidemiological trends.

Clinical Assessment

Disease activity was assessed using:

- **BASDAI** (Bath Ankylosing Spondylitis Disease Activity Index)
- **BASFI** (Bath Ankylosing Spondylitis Functional Index)
- Physician global assessment
- Peripheral joint count
- Enthesitis evaluation

Systemic involvement was defined as the presence of at least one of the following:

- Acute anterior uveitis confirmed by ophthalmologic examination
- Documented inflammatory bowel disease
- Cardiac valvular thickening or conduction abnormalities detected by echocardiography
- Persistent anemia of chronic disease
- Recurrent febrile episodes attributable to inflammatory activity

Laboratory and Instrumental Evaluation

Laboratory parameters included:

- ESR

- CRP
- Complete blood count
- HLA-B27 antigen testing

Imaging studies:

- Radiographs of sacroiliac joints and spine
- Echocardiography
- When indicated, MRI for inflammatory lesions

Statistical Analysis

Descriptive statistics were used for demographic and clinical variables. Continuous variables were expressed as mean ± standard deviation or median (interquartile range). Categorical variables were compared using Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

Patients with systemic manifestations did not significantly differ in age, sex distribution, or disease duration compared to those without systemic involvement. HLA-B27 positivity was present in the majority of patients in both groups, with slightly higher prevalence in the systemic involvement group.

Disease Activity and Functional Status

While BASDAI scores were comparable between groups, patients with systemic involvement demonstrated:

- Increased peripheral arthritis frequency
- Higher rates of enthesitis
- Greater functional impairment reflected by elevated BASFI scores

Interestingly, ESR and CRP levels did not show statistically significant differences between the groups, suggesting that traditional inflammatory markers may not fully capture systemic disease burden.

Peripheral and Axial Involvement

Peripheral arthritis was significantly more common in the systemic involvement group. This supports the hypothesis that systemic manifestations reflect a more generalized inflammatory phenotype rather than isolated axial disease.

Radiographic progression rates did not differ significantly between groups, although patients with systemic involvement tended to exhibit earlier structural changes.

Ocular Manifestations

Acute anterior uveitis was the most frequent systemic feature. Recurrent episodes were observed in a substantial proportion of affected individuals. These patients often required systemic corticosteroids or biologic therapy escalation.

Cardiovascular Findings

Echocardiographic evaluation revealed:

- Aortic root thickening
- Mild valvular regurgitation
- Occasional conduction disturbances

Cardiac involvement, although frequently subclinical, was more prevalent among patients with systemic inflammatory features.

Hematologic and Constitutional Manifestations

Anemia of chronic disease and intermittent febrile episodes were significantly more common in the systemic involvement group, further supporting the concept of increased inflammatory burden.

Treatment Patterns

Patients with systemic involvement required:

- More frequent systemic glucocorticoid therapy
- Higher utilization of biologic agents (TNF inhibitors and IL-17 inhibitors)
- Earlier initiation of advanced therapies

This suggests a more aggressive clinical course requiring intensified treatment strategies.

Discussion

This study confirms that AS should be conceptualized as a systemic inflammatory disorder rather than a purely axial musculoskeletal condition. The presence of multiorgan involvement correlates with a more extensive inflammatory phenotype, greater peripheral joint participation, and increased therapeutic requirements.

Notably, traditional markers such as ESR and BASDAI may underestimate systemic inflammatory burden. Clinical vigilance and multidisciplinary evaluation are therefore essential.

The immunopathogenesis linking axial inflammation to organ-specific manifestations likely involves shared cytokine pathways, particularly TNF-α and IL-17. HLA-B27 misfolding, aberrant immune activation, and gut-joint axis interactions may further contribute to systemic dissemination of inflammation.

The clinical implications are significant:

- Early screening for ocular and cardiac complications
- Personalized therapeutic escalation
- Close monitoring of functional decline

Biologic therapies have transformed disease management; however, optimal timing and selection of agents in patients with systemic features require further study.

Clinical Implications

1. AS management should include routine screening for extra-axial manifestations.
2. Multiorgan involvement indicates a higher inflammatory phenotype.
3. Treatment intensification may be necessary even when BASDAI scores appear moderate.
4. Multidisciplinary care improves long-term outcomes.

Limitations

- Cross-sectional design limits causal inference.
- Single-center data may reduce generalizability.
- MRI was not universally performed.

Longitudinal studies are required to clarify predictive markers of systemic involvement and structural progression.

Conclusion

Multiorgan involvement in ankylosing spondylitis reflects a heightened systemic inflammatory burden and is associated with increased peripheral joint activity, functional impairment, and intensified treatment requirements. Although conventional inflammatory markers may not differ significantly, clinical manifestations reveal a more severe disease phenotype.

Recognition of AS as a systemic immune-mediated condition necessitates comprehensive evaluation beyond axial symptoms. Early identification and targeted management of systemic manifestations are essential to prevent long-term complications and optimize patient quality of life.

Future research should focus on mechanistic pathways linking systemic inflammation to organ-specific damage and on precision-medicine approaches tailored to inflammatory phenotypes within AS.

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