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RESEARCH ARTICLE

The pathogenetic intersection between axial spondylitis and inflammatory bowel diseases: prevalence, risk factors, and clinical implications

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ABSTRACT

Introduction. Axial spondylitis is a chronic inflammatory disease primarily affecting the axial skeleton but can also involve peripheral joints. Axial spondylitis is often associated with extra-articular manifestations, such as inflammatory bowel diseases, emphasizing the need for rigorous monitoring and personalized therapeutic approaches. The interactions between axial spondylitis and inflammatory bowel diseases fall under the concept of "immune-mediated inflammatory diseases", sharing common pathogenetic mechanisms. This study analyzes the prevalence and characteristics of inflammatory bowel diseases in patients with axial spondylitis.

Objective. The objective of this study was to describe the baseline characteristics of patients with axial spondylitis, evaluate the prevalence of inflammatory bowel diseases in this population, and identify correlations between the two conditions, contributing to a better understanding of their pathogenetic and clinical interactions.

Material and methods. This prospective observational study included 257 axial spondylitis patients followed over two years. Patients were selected according to ASAS criteria for axial spondylitis and clinical guidelines for inflammatory bowel diseases. Analyses included clinical evaluations, laboratory tests, and imaging studies. Data were processed using SPSS v22.0. Continuous variables were expressed as mean ± standard deviation or median and interquartile range, and categorical variables as percentages. Correlations were assessed using Spearman's coefficient, with results considered significant at $p<0.05$.

Results. Among the 257 patients included (168 men and 89 women, mean age 48.2 ± 13.1 years), 13.2% were recently diagnosed with axial spondylitis. Of these, 5.1% had inflammatory bowel diseases, distributed as follows: Crohn's disease (3.1%), ulcerative colitis (1.2%), and indeterminate colitis (0.8%). In 53.8% of cases, the diagnosis of inflammatory bowel diseases preceded axial spondylitis. Multivariate analysis identified the absence of a family history of axial spondylitis as a significant risk factor for inflammatory bowel diseases (OR = 3.4; $p = 0.025$). The prevalence of inflammatory bowel diseases increased with axial spondylitis duration, reaching 6.5% in patients with disease progression over eight years.

Conclusions. The study highlights a high prevalence of inflammatory bowel diseases in axial spondylitis patients, indicating the need for rigorous clinical monitoring. The absence of a family history of axial spondylitis was identified as a major risk factor for inflammatory bowel diseases. These findings emphasize the importance of a multidisciplinary clinical approach, including active screening for inflammatory bowel diseases and collaboration between rheumatologists and gastroenterologists, to improve patient prognosis and quality of life.

Keywords: axial spondylitis, inflammatory bowel disease, prevalent, risk factors.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The exact pathogenic mechanisms linking axial spondylitis and inflammatory bowel disease, particularly their shared cytokine path-

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ways and environmental triggers, remain incompletely understood. Additionally, the role of genetic predisposition and the impact of early inflammatory bowel disease management on long-term outcomes in axial spondylitis patients warrant further investigation.

The research hypothesis

Inflammatory bowel disease is more prevalent in patients with ankylosing spondylitis than in the general population, with the absence of a family history of axial spondylitis being a significant predictive factor.

The novelty added by the manuscript to the already published scientific literature

The manuscript adds novelty by highlighting the significant prevalence of inflammatory bowel disease in patients with axial spondylitis, emphasizing the temporal relationship between the diagnoses, with inflammatory bowel disease often preceding axial spondylitis. Additionally, it identifies the absence of a family history of axial spondylitis as a novel risk factor for inflammatory bowel disease, offering new insights into their shared pathogenesis and clinical management.

Introduction

Axial spondylitis (AxS) is part of a group of chronic inflammatory rheumatic diseases that predominantly affect the axial skeleton but may also involve peripheral joints at various stages of disease progression [1, 2]. The prevalence of these conditions is estimated to be approximately 1.5–2% of the general population [1, 3]. AxS is often associated with extra-articular manifestations, such as inflammatory bowel diseases (IBD), along with cardiovascular and renal complications, underscoring the need for rigorous monitoring and personalized therapeutic approaches [2, 4].

From a pathogenetic perspective, AxS is characterized by cytokine dysregulation, similar to that observed in other inflammatory diseases, including IBD [1, 4-6]. While IBD can appear as an associated manifestation of AxS, it may also evolve independently, indicating a complex pathogenetic relationship between the two conditions. These connections fall under the umbrella term "immune-mediated inflammatory diseases" (IMID), reflecting their shared immune mechanisms. Genetic and environmental factors play a central role in the onset and progression of these diseases [3, 5, 7].

Identifying associations between AxS and IBD is crucial for optimizing patient treatment and monitoring. Our prospective observational study, conducted over two years, investigated three cohorts of IMID patients (AxS, IBD, and other associated conditions) to evaluate the prevalence of these conditions.

The aim of this study was to describe the baseline characteristics of patients with AxS and IBD, evaluate the prevalence of IBD within the AxS cohort, and identify potential correlations between these two conditions. This work offers valuable insights into the relationship between these two pathological entities.

Material and methods

The study was designed as prospective observational research with two independent cohorts of patients: one with AxS and the other with IBD. Patients were selected based on their primary diagnosis established at the time of study inclusion. The study was conducted at the clinical base of the Rheumatology and Nephrology Discipline of the Internal Medicine Department at the *Nicolae Testemițanu* University of Medicine and Pharmacy, involving two main clinical specialties: rheumatology and gastroenterology.

Patient enrollment was carried out according to specific inclusion and exclusion criteria. Inclusion criteria: patients aged ≥18 years; diagnosed with AxS (including ankylosing spondylitis, enteropathic arthritis, or undifferentiated spondyloarthritis) or IBD; without other autoimmune inflammatory diseases that could interfere with the primary diagnosis; written informed consent for study participation. Exclusion criteria: patients with multiple IMID diagnoses managed by different specialists, preventing the establishment of a clear primary diagnosis; lack of continuous monitoring by the same specialist during the study.

Patients were recruited from the rheumatology and gastroenterology outpatient clinics of the participating centers and were followed up for two years by the same specialist who enrolled them in the study. Monitoring included clinical evaluations, laboratory tests, and relevant imaging investigations.

Cohort distribution: the AxS cohort comprised patients diagnosed with axial spondylitis or other forms of spondyloarthritis according to ASAS criteria. The IBD cohort included patients with diagnoses of Crohn's disease or ulcerative colitis established per current clinical guidelines. Data were centralized to evaluate interactions between AxS and IBD. Demographic (Table 1) and clinical data were collected for each cohort, ensuring group comparability in terms of age, sex, and disease duration.

The data were processed using SPSS v22.0 statistical software. Continuous variables were expressed as mean ± standard deviation (M ± SD) or median and interquartile range (IQR), while categorical variables were expressed as

percentages. For cohort comparisons, Student's t-test or Mann-Whitney test was used for continuous variables, and Chi-square or Fisher's exact test for categorical variables. Correlations were evaluated using Spearman's coefficient. Results were considered significant at $p<0.05$.

Table 1. Regional distribution of AxS patients in the Republic of Moldova

Region	AxS patients (n = 257)	Percentage (%)
Southern Districts	115	44.7%
- Cahul	53	20.6%
- Taraclia	34	13.2%
- Ciadâr-Lunga	28	10.9%
Northern Districts	51	19.8%
- Edineț	21	8.2%
- Drochia	18	7.0%
- Dondușeni	12	4.7%
Other Regions	91	35.4%

***Note**: The data presented in the table were analyzed using descriptive statistical methods. The absolute number of patients (n) and corresponding percentages (%) were calculated for each region relative to the total AxS cohort (n = 257). The percentages reflect the proportional representation of patients from different geographic districts. Abbreviations:AxS – axial spondylitis.*

This cohort structure and rigorous analytical approach enable a detailed investigation of the relationships between AxS and IBD, contributing to a deeper understanding of these immune-mediated inflammatory diseases. The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (No.5 from 03.03.2020).

Results

Baseline characteristics of patients. The study included 257 patients with AxS, of whom 168 (65.4%) were male and 89 (34.6%) were female. The mean age was 48.2 ± 13.1 years. Only 34 patients (13.2%) were newly diagnosed, while the majority (86.8%) had a known diagnosis of AxS. The median disease duration was 9.1 years (IQR 25–75: 3.5–16.8).

The baseline diagnoses for AxS were as follows: ankylosing spondylitis: 70.1% (n = 180); undifferentiated spondylarthritis: 25.5% (n = 66); enteropathic arthritis: 4.4% (n = 11). 11.0% of patients exhibited extra-articular manifestations associated with AxS (other than IBD), including: conjunctivitis: 5.5% (n = 14); cystitis: 2.5% (n = 6); nail hyperkeratosis: 3.0% (n = 8). Less common manifestations (<1%) included pulmonary fibrosis, aortic insufficiency, and renal amyloidosis.

The family history of AxS was reported in 18.7% (n = 48) of patients. The most frequent comorbidities were depression – 7.8% (n = 20); anemia – 5.1% (n = 13); cardiovascular risk factors – obesity – 21.2% (n = 54); smoking – 27.0% (n = 69); arterial hypertension – 22.8% (n = 58); hypercholesterolemia – 15.7% (n = 40); diabetes mellitus – 5.9% (n = 15).

Frequency of Extra-Articular Immune-Mediated Inflammatory Diseases (IMID). In the cohort of patients with AxS, 112 patients exhibited at least one of these extra-articular manifestations, with a prevalence of 43.6% (95% CI: 37.6–49.6). The most frequent extra-articular manifestation was inflammatory bowel disease (IBD), diagnosed in 13 patients, corresponding to a prevalence of 5.1% (95% CI: 2.8–8.6). Among these, the distribution was as follows: Crohn's disease: 8 patients (3.1%, 95% CI: 1.3–6.1); ulcerative colitis: 3 patients (1.2%, 95% CI: 0.3–3.4); indeterminate colitis: 2 patients (0.8%, 95% CI: 0.1–2.8).

In 7 cases (2.7%, 95% CI: 1.1–5.6), patients exhibited two concurrent inflammatory diseases in addition to AxS.

The prevalence of extra-articular inflammatory manifestations by primary diagnoses is detailed in Table 2. Among patients with axial spondylitis, inflammatory bowel disease was the most frequent extra-articular manifestation, with a prevalence of 3.9% (95% CI: 1.7–7.5). Additionally, all patients with enteropathic arthritis exhibited a form of IBD (100%).

Table 2. Prevalence of most common IBD among different AxS type

Category	Total (n = 257)	Ankylosing spondylitis (n = 180)	Enteropathic arthritis (n = 11)	Undifferentiated AxS (n = 66)
At least one, n (%)	112 (43.6%)	47 (26.1%)	11 (100%)	18 (27.3%)
IBD (any), n (%)	13 (5.1%)	7 (3.9%)	11 (100%)	2 (3.0%)
Crohn's disease, n (%)	8 (3.1%)	4 (2.2%)	7 (63.6%)	1 (1.5%)
Ulcerative colitis, n (%)	3 (1.2%)	1 (0.6%)	3 (27.3%)	0 (0.0%)
Indeterminate colitis, n (%)	2 (0.8%)	2 (1.1%)	1 (9.1%)	0 (0.0%)

***Note**: Patients with other diagnoses were excluded. Data are presented as numbers (n) and percentages (%). Statistical tests used include frequency analysis and Chi-square tests for categorical data. Abbreviations: IBD – inflammatory bowel disease; AxS – axial spondylitis.*

These data underscore the importance of monitoring inflammatory bowel disease in AxS patients, considering its frequency, especially among those with enteropathic arthritis.

Diagnosis chronology and prevalence of inflammatory bowel disease in axial spondylitis. According to the reviewed data, the diagnosis chronology for IBD and AxS is shown in Table 3. In 50% of IBD cases, the diagnosis preceded AxS, with a median of 10 years prior. In another 40% of cases, IBD was diagnosed after AxS, with a median of 9.5 years later. This temporal relationship suggests that IBD may precede or coexist with AxS, emphasizing the need for rigorous monitoring of AxS patients for early detection of IBD.

Table 3. Temporal relationship between AxS and IBD diagnosis

Temporal sequence relative to diagnosis	Before, n (%)	Same year, n (%)	After, n (%)
IBD (n = 13)	7 (53.8%)	1 (7.7%)	5 (38.5%)
Median, years (IQR 25–75)	-10.0 years		9.5 years

***Note**: Data are presented as numbers (n) and percentages (%) or median and interquartile range (IQR). Statistical tests applied include descriptive analysis of temporal distribution. Abbreviations: IBD – inflammatory bowel disease; AxS – axial spondylitis.*

IBD prevalence in different patient subgroups. The study demonstrated that the overall prevalence of IBD in the cohort of AxS patients was 5.1%. Subgroup analysis revealed the following (Table 4):

- The prevalence of IBD was similar between men (5.4%) and women (5.6%), with no statistically significant differences.
- No significant differences were observed between patients with previously known or newly diagnosed AxS regarding IBD prevalence.
- Patients with a family history of AxS had a lower prevalence of IBD (2.4%) compared to those without a family history (7.8%, p = 0.048).
- The prevalence of IBD increased with AxS disease duration: 3.9% in patients with a duration of less than 4 years, 5.1% between 4 and 8 years, and 6.5% in those with a duration of over 8 years.

Table 4. Prevalence of IBD by AxS patient subgroups

Category	IBD prevalence (%)	p
Sex		
Men (n = 168)	5.4%	0.834
Women (n = 89)	5.6%	
AxS diagnosis		
Known (n = 224)	5.8%	0.257
Recent (n = 33)	2.7%	
Family history of AxS		
Yes (n = 48)	2.4%	0.048
No (n = 209)	7.8%	
AxS disease duration		
<4 years (n = 89)	3.9%	0.223
4–8 years (n = 61)	5.1%	
>8 years (n = 107)	6.5%	

***Note**: Data are presented as percentages (%) and include statistical comparisons using Fisher's exact tests (p values). Abbreviations: IBD – inflammatory bowel disease; AxS – axial spondylitis.*

These findings highlight the importance of monitoring inflammatory bowel disease in AxS patients, particularly in those with a longer disease duration and no family history, indicating a potential interaction between these inflammatory conditions.

Multivariable analysis: correlation of variables with the presence of IBD in AxS. To assess variables associated with the presence of IBD in patients with AxS, a multivariable analysis was conducted (Table 5). The analysis included the following variables: age, sex, diagnosis (new or known), family history of AxS, disease duration (<4 years, 4–8 years, ≥8 years), and the presence of other extra-articular manifestations associated with AxS.

The results of the multivariable model demonstrated that IBD prevalence was significantly influenced by the absence of a family history of AxS (OR = 3.4; p = 0.025), suggesting a reduced genetic predisposition for these associated inflammatory conditions.

Beyond family history, other extra-articular manifestations associated with AxS (such as conjunctivitis, balanitis, or nail hyperkeratosis) contributed significantly to the prevalence of IBD. These findings underscore the importance of rigorous monitoring for early detection of IBD, particularly in AxS patients without a family history or typical extra-articular manifestations.

Table 5. Multivariable analysis of factors associated with the presence of IBD

Variable	OR (95% CI)	p
IBD		
Absence of a family history of AxS	3.4 (1.0–15.5)	0.025
Age (per year increase)	Not relevant	Not calculated
Sex (female vs. male)	Not relevant	Not calculated
Disease duration (<4 years vs. ≥8 years)	Not relevant	Not calculated

***Note**: Data are presented as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance (p values) was determined using multivariable logistic regression analysis. Abbreviations: IBD – inflammatory bowel disease; AxS – axial spondylitis.*

These observations complement the previously presented data, confirming that IBD may occur independently of AxS family history and that disease duration does not significantly influence its prevalence. As such, screening for IBD should be included as part of the standard monitoring protocol for AxS patients, regardless of the time since diagnosis.

Discussion

The results of this study demonstrate that a significant proportion of patients with AxS also present with other inflammatory conditions, among which IBD was identified at a prevalence higher than expected in the general population. In our cohort, ankylosing spondylitis was the most frequent form of AxS (65.4%) [2, 5, 8, 9], followed by undifferentiated spondylarthritis (28.8%) and enteropathic arthritis (5.8%) [3-5, 8-10]. This distribution aligns with findings from other studies conducted in hospital-based rheumatology consultations, suggesting that this cohort reflects the profile of patients seen in routine clinical practice [3, 7, 11].

The prevalence of IBD (6.2%) observed in this study is significantly higher than that expected in the general population, estimated at approximately 0.2–0.3%. The most common form was Crohn's disease (3.9%) [1-3], followed by ulcerative colitis (1.9%) [2, 6, 9] and indeterminate colitis (0.4%) [3, 6, 12]. Notably, IBD diagnosis preceded AxS diagnosis in approximately 50% of cases, with a median lead time of 10 years, suggesting a potential pathogenic link between these conditions. In another 40% of cases, IBD was diagnosed after AxS, underscoring the need for monitoring gastrointestinal symptoms in these patients [3-7].

Multivariable analysis revealed that the absence of a family history of AxS is a significant risk factor for developing IBD (OR = 3.4; p = 0.025) [5, 8, 13]. Other variables, such as sex or AxS disease duration, did not significantly influence this model. This suggests that IBD can emerge as a manifestation independent of the genetic mechanisms associated with AxS. Additionally, the presence of other extra-articular manifestations, such as conjunctivitis or nail hyperkeratosis, was associated with an increased prevalence of IBD, indicating a more severe clinical expression of AxS in these patients [2-5, 14, 15].

This study has several important limitations. The data were collected through patient interviews and medical record reviews without incorporating additional diagnostic investigations for active IBD detection. Consequently, some

cases might have been overlooked, leading to an underestimation of the true prevalence [3-5]. Furthermore, patients were recruited from a hospital setting, which might limit the generalizability of these findings to the broader AxS population, as hospital-treated patients tend to have more severe or complex disease forms. Additionally, the predominantly consecutive rather than random inclusion of patients introduces a potential selection bias.

Conclusions

Our study highlights a high prevalence of inflammatory bowel disease in patients with AxS and its association with other extra-articular manifestations. These findings underscore the necessity of an integrated clinical approach for AxS patients, including the monitoring of gastrointestinal symptoms and multidisciplinary collaboration with gastroenterologists. Early identification and management of IBD may contribute to improving patient quality of life and optimizing therapeutic outcomes.

Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (No.5 from 03.03.2020).

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