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Original article

Colonoscopic evaluation in patients with ankylosing spondylitis

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ABSTRACT

Introduction: Patients with ankylosing spondylitis can have intestinal inflammatory lesions, thus the use of colonoscopy for such patients should be defined.
Objectives: To assess the gross intestinal colonoscopic changes and microscopic histopathologic findings of patients with ankylosing spondylitis; to correlate the colonoscopic and histopathologic findings; and to study the relationship of the histopathologic findings with extra-articular manifestations of the disease, HLA-B27, BASFI and BASDAI.
Methods: This is a cross-sectional study of 22 patients with ankylosing spondylitis. The patients underwent clinical assessment, BASDAI and BASFI application, blood collection for HLA-B27 measurement, and colonoscopy with biopsy of four intestinal segments (terminal ileum, right and sigmoid colons, and rectum).
Results: Abnormal colonoscopic results were obtained in 13 (59.1%) patients, the major abnormality being intestinal polyps. The groups of normal and abnormal colonoscopic results (n = 9 and n = 13, respectively) were homogeneous regarding age, BASFI, BASDAI, and categorical variables, and the P-value showed no significant difference between groups. The histopathological findings revealed abnormal biopsies in 81%, 90.9%, 90.9% and 86.4% for terminal ileum, right colon, sigmoid colon, and rectum, respectively. The histopathologic results showed no statistically significant association with the extra-articular manifestations, BASFI, BASDAI and HLA-B27 positivity.
Conclusions: The histological analysis of the four intestinal segments evidenced inflammatory lesions in patients with normal and abnormal colonoscopic results, independently of bowel symptomatology and therapy used in the treatment of the basal disease.

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Avaliação colonoscópica em pacientes com espondilite anquilosante

Palavras-chave:
Espondilite anquilosante
Colonoscopia
Análise histológica
Alteração intestinal
Doença inflamatória intestinal

RESUMO

Introdução: Pacientes com espondilite anquilosante podem apresentar-se com lesões inflamatórias intestinais, e, por isso, deve ser definido o uso da colonoscopia para tais pacientes.
Objetivos: Avaliar as alterações colonoscópicas intestinais macroscópicas e achados histopatológicos microscópicos de pacientes com espondilite anquilosante; correlacionar os achados colonoscópicos e histopatológicos; e estudar a relação dos achados histopatológicos com as manifestações extra-articulares da doença, HLA-B27, BASFI and BASDAI.
Métodos: Este é um estudo transversal de 22 pacientes com espondilite anquilosante. Os pacientes passaram por uma avaliação clínica, BASDAI e BASFI, coleta de sangue para determinação de HLA-B27, e colonoscopia com biópsia de quarto segmentos intestinais (íleo terminal, cólon direito, cólon sigmoide e reto).
Resultados: Resultados colonoscópicos anormais foram obtidos em 13 (59,1%) pacientes, e a principal anormalidade foi a presença de pólipos intestinais. Os grupos de resultados colonoscópicos normais e anormais (n = 9 e n = 13, respectivamente) foram homogêneos no que diz respeito à idade, BASFI, BASDAI, e variáveis categóricas, e o valor P não revelou diferença significativa entre grupos. Dos resultados histopatológicos, 81% tiveram uma biópsia anormal do íleo terminal, 90.9% tiveram uma biópsia anormal do cólon sigmoide, e a biópsia retal estava anormal em 86.4%. Os achados histopatológicos revelaram biópsias anormais em 81%, 90.9%, 90.9% e 86.4% para o íleo terminal, cólon direito, cólon sigmoide e reto, respectivamente. Os resultados histopatológicos não revelaram associação estatisticamente significativa com as manifestações extra-articulares, BASFI, BASDAI e positividade para HLA B27.
Conclusões: A análise histological dos quatro segmentos intestinais evidenciou lesões inflamatórias em pacientes com resultados colonoscópicos normais e anormais, independentemente da sintomatologia intestinal e do tratamento usado para a doença basal.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by involvement of the axial skeleton, entheses and, less commonly, peripheral joints. AS is cause of inflammatory back pain due to involvement of the sacroiliac joints and the spine, which can result in ankylosis.[1] In addition to damage to the axial skeleton and peripheral joints, AS may also present extra-articular manifestations, such as uveitis and cardiac and pulmonary manifestations.[2]

Subclinical intestinal inflammation can occur in AS, which can be observed through ileocolonoscopy in 25%-49% of cases. Microscopic lesions, detected by intestinal biopsy, are more frequent than gross lesions, being observed in 50%-60% of patients and histologically classified as acute or chronic.[3] Chronic injuries are more common, occurring in 80% of patients and with similar characteristics to the ileocolitis of Crohn's disease (CD). It is suggested that the intestinal mucosa plays an important role in the pathogenesis of spondyloarthritides, through the possible permeability to exogenous antigens.[3,4]

The aim of this study was to evaluate the prevalence of bowel inflammation in patients with AS through colonoscopy, besides possible associations with clinical and functional aspects inherent to the underlying disease.

Patients and methods

Study design

A cross-sectional study was conducted with 22 patients diagnosed with AS followed at the spondyloarthritis outpatient clinic, Hospital Universitario Clementino Fraga Filho (HUCFF), Universidade Federal do Rio de Janeiro (UFRJ). All participants read and signed the Informed Consent Form (ICF) provided, in accordance with the standards of the institution's Research Ethics Committee (REC).

Inclusion criteria

Patients diagnosed with AS defined by New York Criteria (1984).[5]

Exclusion criteria

Patients with a previous diagnosis of CD and ulcerative colitis; presence of non-absorptive syndromes, celiac disease among them; concomitant diagnosis of toxic megacolon, acute diverticulitis, acute perforative abdomen, recent myocardial infarction (last 6 months), recent pulmonary embolism (last 6 months), pregnancy, neutropenia and use of anticoagulants (warfarin).

Procedures performed

Data, such as age, gender, race, extra-articular manifestations of the disease, among others, were collected from the clinical evaluation performed with patients.

To characterize the clinical activity of the disease and of physical work capacity of the sample, patients were submitted to the use of two instruments: the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[6] which address issues referring to clinical symptoms of the disease, as well as limitations for specific activities, allowing their graduation.

Examinations

Blood collections were performed for HLA-B27 determination in the Clinical Analysis Laboratory, UFRJ, with a fasting period of 8 hours, using the surface phenotyping technique and the cellular technique with anti-HLAB27/B7 by flow cytometry.

Patients underwent colonoscopy with biopsy, in order to assess the presence of intestinal lesions in the colon; concomitantly, histopathological analysis of bowel was carried out, through the collection of biopsy material in 4 pre-defined sites: terminal ileum, ascending colon, colon sigmoid and rectum. Inflammatory lesions were classified by inflammation degree (mild, moderate and severe).

Statistical analysis

To test the significance of the tests mentioned above, the following statistical methods were applied:1. To compare numerical data between independent samples, Student's *t* test or the Mann-Whitney test (non-parametric) was used. The variance homogeneity was tested by the Levene's test;2. To compare proportions (categorical data) the chi-squared (χ^2) or Fisher's exact test was used;3. A logistic regression analysis was performed to identify the independent baseline variables that influence (or predict) the change of the colonoscopy outcome.

Non-parametric methods were used, because some variables did not present a normal distribution (Gaussian distribution) due to the wide dispersion and of the rejection of the hypothesis of normality, according to the Kolmogorov-Smirnov test. A level of 5% as a criterion for determining significance was adopted. The statistical analysis was performed with statistical software IBM SPSS Statistics, version 19.

Results

Of the 22 patients included, 19 (86.4%) were male, and 11 patients (50%) were classified as Caucasians (Table 1). The mean age of the study population was 45.9 ± 10.9 years (Table 2). With regard to pathological features of AS in the sample studied, 6 patients (27.3%) had some extra-articular manifestation, and its most prevalent expression was anterior uveitis, present in 5 patients (22.7%) (Table 1).

As for the characterization of clinical disease activity, as well as the functional capacity of the patients, the sample was subjected to instruments for evaluation of the disease, among them, respectively, BASDAI and BASFI. The mean BASDAI was 3.6 ± 1.5; and BASFI showed a mean of 4.6 ± 1.8 (Table 2).

All patients underwent blood collection with HLA-B27 dosage, and 9 patients (40.9%) were positive for this marker. The remaining samples showed negative or indeterminate HLA B27 (Table 1).

As to the analysis of the pharmacological profile of the studied sample, one can see a predominance of the use of anti-TNF agents, with this class of medication instituted in 17 patients (77.3%). The most widely used anti-TNFs were infliximab and etarnecept, both prescribed for 7 patients each. Adalimumab was prescribed for 3 patients. In 9 patients (40.9%), the anti-TNF agent was used as monotherapy, and in 8 patients (36.4%) it was used in combination with a DMARD,

Table 1 – General description of basal categorical variables.

Variable	n	%
Gender		
Female	3	13.6
Male	19	86.4
Race (caucasians)	11	50.0
HLA-B27		
Positive	9	40.9
Undetermined	4	18.2
Negative	9	40.9
Presented extra-articular change	6	27.3
Presented ocular change	5	22.7
Presented no kidney change	22	100.0
Presented cardiac change	1	4.5
Presented no neurological change	22	100.0
Presented no pulmonary change	22	100.0
Colonoscopy		
Normal	9	40.9
Abnormal	13	59.1
Sigmoid colon biopsy		
Normal	2	9.1
Abnormal	20	90.9
Mild inflammation	17	77.3
Moderate inflammation	2	9.1
Severe inflammation	1	4.5
Terminal ileum biopsy		
Normal	4	18.2
Abnormal	17	81.0
Mild inflammation	4	18.2
Moderate inflammation	5	22.7
Severe inflammation	8	36.4
Right colon biopsy		
Normal	2	9.1
Abnormal	20	90.9
Mild inflammation	17	77.3
Moderate inflammation	2	9.1
Severe inflammation	1	4.5
Rectal biopsy		
Normal	3	13.6
Abnormal	19	86.4
Mild inflammation	14	63.6
Moderate inflammation	4	18.2
Severe inflammation	1	4.5

Table 2 – Analysis of categorical and numeric variables according to change in colonoscopy examination.

Categorical variable	Colonoscopy, normal (n = 9)		Colonoscopy, abnormal (n = 13)		P-value
	n	%	n	%	
Male	8	89%	11	85%	0.774
Caucasians	5	56%	6	46%	0.665
HLA-B27[1] negative	5	56%	4	31%	0.489
Absence of:					
Extra-articular change	8	89%	8	62%	0.157
Ocular change	8	89%	9	69%	0.279
Cardiac abnormality	9	100%	12	92%	0.394
Abnormal results					
Sigmoid colon biopsy	8	89%	12	92%	0.784
Terminal ileum biopsy	7	88%	10	77%	0.549
Right colon biopsy	8	89%	12	92%	0.784
Rectal biopsy	8	89%	11	85%	0.774

methotrexate being the most used in combination therapy, followed by sulfasalazine.

When evaluating patients undergoing colonoscopy, 9 had normal results, and 13 had abnormal results, forming two groups: normal colonoscopy (n = 9) and abnormal colonoscopy (n = 13).

In patients with abnormal colonoscopy, the main colonoscopic finding was the presence of intestinal polyps, which were present in 6 patients. Of the 6 patients with intestinal polyps, 5 showed polyps classified as of the sessile type, and 1 showed a pedunculated polyp. The most common location of polyps was in the sigmoid colon. The histopathological analysis of polyps excluded the presence of malignancy, and only 1 patient had a tubular adenoma. Comparing the 2 groups formed (normal and abnormal colonoscopy), it can be seen that, with respect to the baseline numerical analyses, both groups showed homogeneity in the aspects related to age, BASFI and BASDAI (Table 2). According to the P-value presented, the numerical variables showed no significant difference between the colonoscopy results. As for the analysis of categorical variables, when comparing the 2 groups, one can also notice that both were homogeneous.

Among the 22 patients, 17 (81%) had alteration in the terminal ileum biopsy, and in 8 (36.4%) there was a marked inflammation. Twenty patients (90.9%) had alteration in the right colon biopsy, and 17 (77.3%) had histopathology consistent with mild inflammation. The histopathological evaluation of the sigmoid colon showed abnormality in 20 patients (90.9%), and 17 (77.3%) were classified as presenting mild inflammation. In the rectum, the analysis by biopsy showed changes in 19 patients (86.4%), with mild inflammation in 14 patients (63.6%) (Table 1).

By analyzing the sigmoid colon biopsy, 2 patients had results considered normal and 20 patients had an abnormal report, with prevalence of a mild inflammation pattern (Table 3). There was no statistical significance between the 2 groups analyzed, as the group with abnormal biopsy had a predominant number of patients. All patients who had some type of inflammation in the sigmoid colon biopsy showed alterations also in the right colon (p = 0.000) and rectal (p = 0.000) biopsies at the level of significance of 5%.

With respect to the histological evaluation of the terminal ileum, 1 patient was excluded from the analysis because no biopsy of that site was performed; 4 patients had normal results, and 17 were considered abnormal (Table 4). In the group with abnormal biopsies, it was mainly observed an accentuated microscopic inflammation. According to the P-value presented, the variables showed no significant difference between the results of the terminal ileum biopsies.

In the analysis of the right colon biopsy, 20 patients had their biopsy classified as abnormal, with preponderance of mild inflammation, and this should be considered as the most frequent type of inflammation during the group's analysis. Patients with any type of inflammation during right colon biopsy showed abnormalities in the rectal biopsy (P = 0.000) at the level of significance of 5%. According to the P-value presented, the baseline numerical and categorical variables were not statistically significant in the analysis for the groups of right colon biopsy (Table 5).

In the evaluation of the rectal biopsies, 19 patients presented biopsy with an altered result, and 3 patients were classified as normal results (Table 6). There was predominance of mild inflammation. According to the P-value shown, there is a tendency for the abnormal group of greater BASDAIs compared to the normal group. In addition, there is a trend for fewer extra-articular changes (P = 0.099) at a 10% level for those patients who had some type of inflammation in the rectal biopsy, contrary to the gross colonoscopic findings.

Discussion

AS affects men and women at a ratio of 2:1 around the 3rd decade of life,[7] and 90% of patients are positive for HLA-B27;[8] In this study, the prevalence of AS was also higher in men *versus* women, occurring at a ratio of 6:1, but HLA-B27 positivity was found in 40.9% of patients. Van Praet *et al.*[13] evaluated 65 patients with AS undergoing colonoscopy; these authors also showed no association of microscopic intestinal inflammation with positivity for this antigen.

Anterior uveitis is the main extra-articular manifestation of AS, being more common in men, affecting 25% to 40% of

Table 3 – Analysis of baseline categorical variables according to the result of the sigmoid colon biopsy.

Variable	Sigmoid colon biopsy, normal (n = 2)		Sigmoid colon biopsy, abnormal (n = 20)		P-value[a]
	n	%	n	%	
Male	2	100%	17	85%	0.556
Caucasians	1	50%	10	50%	1.000
HLA-B27 negative	1	50%	8	40%	0.783
Absence of:					
Extra-articular change	1	50%	15	75%	0.449
Ocular change	2	100%	15	75%	0.421
Cardiac abnormality	1	50%	20	100%	0.001
Abnormal results					
Terminal ileum biopsy	1	50%	16	84%	0.241
Right colon biopsy	0	0%	20	100%	0.000
Rectal biopsy	0	0%	19	95%	0.000

[a] Chi-Squared (χ^2) test.

Table 4 – Analysis of baseline categorical variables according to the result of the terminal ileum biopsy.

Variable	Terminal ileum biopsy, normal (n = 4)		Terminal ileum biopsy, abnormal (n = 17)		P-value[a]
	n	%	n	%	
Male	4	100%	14	82%	0.364
Caucasians	1	25%	9	53%	0.314
HLA-B27 negative	1	25%	7	41%	0.215
Absence of:					
Extra-articular change	3	75%	12	71%	0.861
Ocular change	3	75%	13	76%	0.950
Cardiac abnormality	4	100%	16	94%	0.619
Abnormal results					
Terminal ileum biopsy	3	75%	16	94%	0.241
Right colon biopsy	3	75%	15	88%	0.496
Rectal biopsy					

[a] Chi-Squared (χ^2) test.

patients, with 90% of these testing positive for HLA-B27.[9–11] In the present study, our data were near those in the literature, and 27.3% of patients had some type of extra-articular manifestation of the disease, anterior uveitis being the more prevalent and present in 5 patients (22.7%). Of these 5 patients, 4 were male, and 4 were positive for HLA B27. In 2006, Rudwaleit studied colonoscopies of patients with AS and showed that subclinical gross intestinal inflammation was present in 25%-49% of patients;[3] however, in this study the subclinical gross inflammatory lesions characterized by the presence of ileal inflammation were found in only 2 patients (9.09%).

It is known that in patients with AS and submitted to colonoscopy, the microscopic inflammatory lesions, detected in 50%-60% of cases by intestinal biopsy, are more prevalent

Table 5 – Analysis of baseline categorical variables according to the result of the right colon biopsy.

Variable	Right colon biopsy, normal (n = 2)		Right colon biopsy, abnormal (n = 20)		P-value[a]
	n	%	n	%	
Male	2	100%	17	85%	0.556
Caucasians	1	50%	10	50%	1.000
HLA-B27 negative	1	50%	8	40%	0.783
Absence of:					
Extra-articular change	1	50%	15	75%	0.449
Ocular change	2	100%	15	75%	0.421
Cardiac abnormality	1	50%	20	100%	0.001
Abnormal results					
Rectal biopsy	0	0%	19	95%	0.000

[a] Chi-Squared (χ^2) test.

Table 6 – Analysis of baseline categorical variables according to the result of the rectal biopsy.

Variable	Rectal biopsy, normal (n = 3)		Rectal biopsy, abnormal (n = 19)		P-value[a]
	n	%	n	%	
Male	3	100%	16	84%	0.459
Caucasians	1	33%	10	53%	0.534
HLA-B27 negative	1	33%	8	42%	0.537
Absence of:					
Extra-articular change	1	33%	15	79%	0.099
Ocular change	2	67%	15	79%	0.637
Cardiac abnormality	2	67%	19	100%	0.010

[a] Chi-Squared (χ^2) test.

if compared to gross lesions, being usually asymptomatic.[3] In 2009, Hascelik *et al.*[12] studied 25 patients with a diagnosis of AS, which underwent colonoscopy with biopsy. In their analysis, these authors also found a higher prevalence of histological bowel inflammatory lesions, and microscopic intestinal inflammation was found in 20 of 25 patients (80%), with more prevalence in the ileum. In 2013, Van Praet *et al.*[13] evaluated 65 patients with AS and showed microscopic intestinal lesions in 46.9% of their patients, particularly of the chronic type and with a preferential location in the ileum.

Corroborating data from the literature, in our study the microscopic inflammatory lesions were also more prevalent than gross lesions, being present in all 4 intestinal segments analyzed, even in patients with normal colonoscopic findings. In our analysis, we observed a predominance of chronic-type lesions with some degree of inflammation in over 80% of the biopsies of each intestinal segment (Table 1), exceeding the data on the prevalence of intestinal inflammation in previously reported studies. Mild inflammation predominated in the sigmoid colon, right colon and rectum, even in patients taking disease-modifying drugs and anti-TNFα medications. Severe inflammation predominated in the terminal ileum, irrespective of the therapy used for AS. This fact is an additional element that supports one of the pathophysiological theories of AS, which suggests that the intestinal mucosa is considered as a initial pathological site of the disease, occurring local presentation of pathogenic antigens to T lymphocytes CD8, with their subsequent circulation to joints through adhesive molecules.[3,14]

In AS, in patients with chronic inflammatory intestinal lesions evidenced by histological analysis of the colon, there is a stronger association between the presence of intestinal inflammation with clinical activity of AS.[3,4,12] Van Praet *et al.*[13] evaluated 65 patients with AS showing association between microscopic intestinal inflammation with disease activity, as measured by BASDAI. This fact was not proven in our analysis, where a significant statistical relationship between the suggestive clinical parameters of disease activity and functional capacity of patients (i.e. BASFI and BASDAI) was not confirmed by the results presented.

Contrary to what we observed in our analysis, Hascelik studied 25 patients with a diagnosis of AS,[12] who underwent colonoscopy with biopsy and a preliminary assessment of demographic and clinical parameters, including BASDAI and BASFI. In his analysis, Hascelik also found a higher prevalence of histological inflammatory bowel lesions with presence of microscopic intestinal inflammation in 80% of cases, more prevalent in the ileum. Furthermore, patients with gross intestinal lesions had higher disease activity, characterized by BASDAI.

The small size of our sample was a limiting factor that may justify, in this study, the absence of a statistically significant correlation among the clinical characteristics of AS (assessed by BASFI and BASDAI), and laboratory data (HLA-B27 positivity) with the histological data presented, which suggested the presence of microscopic intestinal inflammation in intestinal segments examined by colonoscopy.

As regards the influence of medications in the induction of colonic inflammatory lesions, the literature is scarce in terms of data showing the involvement of DMARDS and anti-TNF drugs. One point that should be questioned would be the fact that the use of anti-TNF agents is masking the colonoscopy and histology reports, by preventing the emergence of the characteristic lesions, since this type of medication also has its indication for the treatment of patients with CD and ulcerative rectocolitis (URC). There are no data in the literature addressing the influence of anti-TNF in both gross and microscopic intestinal lesions in patients with AS.

Conclusion

In the present study, the colonoscopic changes in patients with ankylosing spondylitis are the same as those found in the general population, confirming the polypoid lesions as the most prevalent, and not justifying the routine use of colonoscopy. The bowel histological analysis showed inflammatory lesions in all four segments biopsied, regardless of the colonoscopic report, intestinal symptomatology and therapy used for the underlying disease.

Conflicts of interest

The authors declare no conflicts of interest.

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