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RECTOSIGMOID INFLAMMATORY LESIONS AND ITS DETERMINANTS IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Keywords:

Inflammatory rectosigmoid lesions, IBD,risk factors, ankylosing spondylitis.

Abstract

Introduction: Ankylosing Spondylitis (AS) is a chronic and systemic inflammatory disease which mainly affects the axial skeleton. There are substantial evidences that risk of rectosigmoid inflammation is increased in patients with AS. Subclinical inflammation could be associated with significant complications; understanding of its prevalence is an important step towards (developing measures to improve) both early diagnosis and selection of the most appropriate treatment strategies. We have studied the prevalence of the rectosigmoid inflammation and its associated risk factors in patient with AS.

Materials and Methods: In this cross-sectional study ,110 patients who have the diagnosis of AS based on the Assessment of New York classification where enrolled. The severity of AS based on AS disease activity (ASDAS-CRP) Score was also calculated. Patients who were on biological agents or Sulfasalazine were excluded. Written informed consent was obtain from all patients. Demographic data, smoking history, time since diagnosis, disease severity, axial versus axial and peripheral involvement, HLA B27 status, latest CRP and ESR level and also fecal Calprotectin were collected. All patients underwent rectosigmoidoscopy and biopsy. Data analysis was done using SPSS software(Ver 18).

Results: 87(79.1%) patients were male and 23(20.9%) were females. The mean age was 41.46±11.81. year. The mean time since diagnosis was 6.49±7.16 year.. 54.5% of patients were non-smoker. 84% of patients had other organs involvement. Out of 110 patients, 57(51.8%) had axial only and the rest had both axial and peripheral involvement. Calprotectin level was increased in 94% of patients and the mean level was92.81±40.7. The mean CRP and ESR level was 34.22±25 and 35.89±25.54 respectively. 39.1% of patients were HLA27 positive. Severity of AS in most of patients was in intermediate range (36.4%). In 37 patients(33.6%) the rectosigmoid macroscopically looked abnormal. The microscopic assessment of the samples showed inflammatory bowel disease in 15.5%, chronic non-specific inflammationin 49.1% and was normal in 31.8%. There was a significant relationship between age,CRP,fecal calprotectin and macroscopic and microscopic findings (p value for age: 0.001 and 0.005), (p values for fecal calprotectin: 0.0001 and 0.008), (pvalues for CRP :0.0001 and 0.008). The relationship between macroscopic findings and severity of AS (p value 0.008) and time since diagnosis (p value 0.015) was statistically significant.

Conclusion: This study showed that older age, severity of AS, high fecal Calprotectin level and high CRP are associated with presence of inflammatory rectosigmoid disease and could be used as a important determinant for early diagnosis of this lesion in patients with AS.

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Introduction

Ankylosing Spondylitis (AS) is a chronic inflammatory disease which mainly involves axial skeleton and usually presents with back pain and gradual stiffness of vertebral column. Other organs including gastrointestinal tract, eyes and heart may also become affected. (1,2)It particularly affects young people (peak age 20-30) and is twice as common in men than women. (3). Its prevalence varies between 0.1-1.2 per cent (4)

Different studies have shown that Ankylosing Spondylitis is associated with increased risk of inflammatory rectosigmoid disease (5-6) including ulcerative colitis which almost always involves rectum. This is diagnosed with rectosigmoidoscopy. (7)

Inflammatory bowel disease(IBD) and ankylosing spondylitis (AS) are similar chronic inflammatory disease whose definitive etiology is unknown.Although both appeare to be distinct and well-defined phenotypes,there is increasing clinical and genetic evidence supporting an intertwined pathogenic relationship.(8)Histological analyses of gut biopsies in AS patients have observed evidence of microscopic gut inflammation even more frequently with a prevalence of 50 to 60% (9).Alternatively,sacroiliac changes similar to those seen in AS have been noted in 10 to 20% of patients with the primary diagnosis of IBD and 7to 12% of IBD patients carry the concomitant diagnosis of AS(10).The genetic susceptibility risk is high in both conditions and recent studies with large and well-characterized cohorts support an important genetic overlap between AS and IBD.(11)

Mucosal dysregulation may be an important pathway linking genetic susceptibility to invironmental triggers in both conditions.Patients with IBD and AS both have increased intestinal permeability as shown by the Cr-ethylenediamine tetraacetic acid resorption test (12)loss of tolerance to normal bowel flora as evidenced by an increase in circulating antibodies to certain bacterial antigen has been observed in IBD,including anti-saccharomyces cerevisias mannan antibodies (ASCA),anti –Escherichia coli outer membrane porin c(OMPC) and anti anti-CBir1 flagellin AB(13). The same IBD associated serologic markers present at a greater frequency and at a higher titer in AS patients compared with healthy controls, indicating a potential loss of tolerance to commensal bacteria similar to that observed in IBD patients (13)

Calprotectin is a neutrophil –derived protein that can be quantified in the feces and has become estabilished as a marker of whole gut inflammation.The increase of fecal calprotectin seen in the stool of IBD patients is a direct result of increased neutrophil migration into the gut lumen across inflamed mucosa.(14) Different studies have shown that fecal calprotectin are found in higher percentages of AS patients compared with healthy controls.(10)

Anti –TNF agents are of particular relevance to AS patients with concomitant IBD as treatment of back pain and other rheumatic symptoms with NSAIDs poses the patient at some risk of exacerbation of underlying IBD. In IBD,infliximab,unlike etanercept,is effective in treating clinical symptoms,including and maintaining remission,and mucosal healing.Adalimumab also appears to be effective in treating both AS and IBD.Currently, infliximab is the drug of choice for the treatment of patients with active AS associated with IBD(15)

Most patients with AS rapidly respond to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)(7). A number of studies using different methodologies have evaluated the potential deleterious effects of NSAIDs on the small bowel and colon. Considered together, they suggest that NSAID-related intestinal injury is common. The gut is a potential site for a variety of NSAID-induced injuries including erosions, ulcers,strictures, and perforation , which can lead to bowel obstruction(16-17). NSAIDs can also lead to colitis resembling inflammatory bowel disease (IBD), or exacerbate preexisting IBD (18- 19). A high local concentration of an active NSAID following ingestion seems to be necessary to increase intestinal permeability, which appears to be a prerequisite for NSAID-induced enteropathy (20).

A relationship between inflammatory gut lesions and spondyloarthritis has been demonstrated by many authors(21-22-23).Subclinical inflammatory gut lesions can be founde in patients with spondyloartheritis.In studies performed in Belgium and Scandinavia,macroscopic and microscopic changes have been identified in patiens with spondyloartheritides in up to 50%(24).In most of this studies,the study population was heterogeneous consisting of different type of spondyloartheritides.which might have introduced some sampling bias.

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We undertook the present study to assess macroscopic and microscopic changes in the rectosigmoid mucosa of AS patients only.we also assess the determinants of inflammatory lesions in patients with ankylosing spondylitis.

Material and Methods

We evaluated 110 patients who had the diagnosis of AS based on New York criteria. Patients who had a previous diagnosis of IBD or have been treated with Sulfasalazine or biological agents or were not able to undergo rectosigmoidoscopy were not included in the study. All patients after consenting to participate in the study were given a questionnaire which included their age, gender, smoking history and time since diagnosis. The severity of AS based on AS disease activity (ASDAS-CRP) Score was also calculated. In all patients ESR, CRP, fecal Calprotectin level and HLAB27 status were measured. A gastroenterologist performed rectosigmoidoscopy in all patients and 5-6 biopsies were taken from rectum and sigmoid . The samples were then examined by pathologist and were macroscopically classified as 0 (normal findings), 1 (erythema and inflammation of mucosa), 2 (small ulcer), 3 (mucosal edema, ulcer and bleeding), 4 (ulcer, bleeding and bowel stricture). Microscopic classification included: normal (small number of lymphocytes and plasmocytes in lamina propria with no granulocytes), minimal invasion(small number of lymphocytes and plasmocytes in lamina propria with a few granulocytes),mild to moderate inflammation (many lymphocytes and plasmocytes and invasion of granulocytes into the crypts.,partial glandular atrophy(crypt dilatation and microgranulation in lamina properia),neoplastic change(cellular polymorphism and nucleus with hypercromatism and mitosis),IBD(crypt disruption and abceses).

Based on macroscopic and microscopic findings, patients were divided into four groups of normal, chronic non-specific inflammation, IBD and others. Data were assessed using SPSS 18 which also performed data checking and data cleaning. Skewed variables were transformed to normally distributed variables and data were analysed using T-test or one way ANOVA test. Categorical variables were analysed using Ki-Square and Fisher test. Regression logistic was used to evaluate the roles of different variable to predict rectosigmoid inflammation.

Results

Out of 110 patients, 87 (79.1%) were male and 23 (20.9%) were female. 32.7% of patients were between 41 and 50 years of age. Mean age was 41.46 +/- 11.81years. Youngest patient was 21 and oldest was 67 years old. Mean duration of the disease was 6.49 +/- 7.16 years. The shortest duration of the disease was around a month and the longest was 30 years. 51.8% only had axial disease while 48.2 % had both axial and peripheral disease. Seventeen patients (15.5%) had extra-axial disease. The disease severity was mild in 39 patients,(35.5%). 31 patients(%) were current smoker, 9 were ex-smoker and 60 patients had never smoked before. The average number of pack years of smoking amongst ever-smokers was 6.02 +/- 3.64 (between 2 and 20 pack years). 43 patients (39.1%) had positive HLAB27. Mean Fecal Calprotectin level was 92.81 +/- 40.7µgr/gr. (The lowest level was 5 and the highest level was 200). Mean CRP level was 34.22 +/- 25.54 (range between 4 and 110). Mean ESR level was 35.89 +/- 26.06. (range 8-120).

Macroscopical view of rectosigmoid in 73 patient (66.4%) was normal and in 37 patients (33.6%) was abnormal. 75 patients(68.2%) had abnormal microscopic finding. The most common macroscopic abnormality included erythema and inflammation of mucosa (grade 1). (25.5%)
Macroscopic and microscopic features of the rectosigmidoscopic examination and related variables have been shown in Table 1 and 2, respectively. .

The association between mean age of patients(P=0.001) fecal calprotectin level (P=0.001), severity of AS (P= 0.008), mean duration of the disease(P=0.015), CRP level(P values 0.0001), and macroscopic lesions on rectosigmoidoscopy was statistically significant.

There is a significant relationship between mean age of patients (P=0.004) , CRP level (p=0.008)and presence or absence of microscopic (P=0.004) inflammatory lesions.

Role of different variables on macroscopic and microscopic lesions using the regression logistic model has been shown in tables number 3 and 4.

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Older age was associated with increased likelihood of abnormal microscopic and macroscopic lesions (P=0.023) AS severity increased possibility of abnormal macroscopic lesions. More severe disease increased the likelihood of abnormal macroscopic lesions by 5.8 times compared to less severe disease. Also highly severe AS was associated with 14.7 times increase in the likelihood of abnormal macroscopic lesions compared to moderately severe AS.

Adjusted variables analysis also showed that high CRP and high fecal Calprotectin are the only variables which were significantly related to abnormal microscopic lesions. High Fecal Calprotectin level was associated with 2.8 times increase in presence of abnormal microscopic lesions. High CRP also increased presence of abnormal microscopic lesions by 8.1.

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Table1: Microscopic features of the rectosigmidoscopic examination and related variables

Microscopic lesions / Patients		Abnormal		Normal		Total		P value
		N	%	N	%	n	%	
Gender	Male	56	64.4	31	35.6	87	100	p=0.0095
	Female	19	82.6	4	17.4	23	100	
Cigaret smoking	No	39	65	21	35	60	100	p=0.0095
	Yes	36	72	14	28	50	100	
GI symptoms	No	17	73.9	6	26.1	23	100	P=0.5
	Yes	58	66.7	29	33.3	87	100	
Type of articular involvement	Axial	42	73.7	15	26.3	57	100	p=0.199
	Axial and pripheral	33	62.3	20	37.7	53	100	
Fecal calprotectin level	Normal	14	87.5	2	12.5	16	100	P=0.087
	High	61	64.9	33	35.1	94	100	
CRP level	CRP high	61	81.3	14	18.7	75	100	p=0.0001
	CRP normal	14	40	21	60	35	100	
ESR level	ESR high	36	69.2	16	30.8	52	100	P=0.82
	ESR norma	39	67.2	19	32.8	58	100	
HLAB27	HLAB27positive	29	67.4	14	32.6	43	100	p=0.89
	HLAB27negative	46	68.7	21	31.3	67	100	
AS severity	Mild	30	76.9	9	23.1	39	100	P=0.087
	moderate	22	55	18	45	40	100	

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Table2: Macroscopic features of the rectosigmidoscopic examination and related variables

Macroscopic lesions / Patients		Abnormal		Normal		Total		P value
		n	%	N	%	n	%	
Gender	Male	30	34.5	57	65.5	87	100	p= 0.71
	Female	7	30.4	16	59.6	23	100	
Cigaret smoking	No	19	31.7	41	68.3	60	100	p= 0.68
	Yes	18	36	32	64	50	100	
GI symptoms	No	9	39.1	14	60.9	23	100	p= 0.53
	Yes	2	32.2	59	67.8	87	100	
Type of articular involvement	Axial	20	35.1	37	64.9	57	100	p= 0.73
	Axial and pripheral	17	32.1	36	67.9	53	100	
Fecal calprotectin Level	normal	0	0	16	100	16	100	p= 0.001
	High	37	39.4	57	60.6	94	100	
CRP Level	CRPhigh	31	41.3	44	58.7	75	100	p=0.012
	CRP Normal	6	17.1	29	82.9	35	100	
ESR Level	ESR High	18	34.6	34	65.4	52	100	p=0.83
	ESR normal	19	32.8	39	67.2	58	100	
HLAB27	HLAB27positive	16	37.2	27	62.8	43	100	p= 0.52
	HLAB27negative	21	31.3	46	68.7	67	100	
AS severity	Mild	12	30.8	27	69.2	39	100	p= 0.008
	moderate	8	20	32	80	40	100	
	severe	17	54.8	14	45.2	31	100	

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Table3: Role of different variables on macroscopic lesions using the regression logistic model

	B	df	Sig.	Odds Ratio	95.0% C.I.for EXP(B)	
					Lower	Upper
Gender(male)	.104	1	.895	1.110	.235	5.240
Age(years)	-.061	1	.023	.941	.892	.992
Time since of presence(year)	-.034	1	.375	.967	.897	1.042
Cigaret smoking	-.790	1	.241	.454	.121	1.698
GI symptom present	.299	1	.632	1.349	.396	4.595
Axial joint involvement	-.079	1	.891	.924	.301	2.842
High fecalcalprotectin level	22.210	1	.998	4.420	.000	.
CRP high	.992	1	.141	2.696	.720	10.097
ESR high	.378	1	.545	1.459	.429	4.961
sever As severity		2	.016			
moderateAS severity	1.967	1	.012	7.146	1.544	33.073
Mild AS severity	2.148	1	.007	8.567	1.777	41.313
Constant	.653	1	.787	1.922		

Table4:Role of different variables on microscopic lesions using the regression logistic model

	B	df	Sig.	Odds Ratio	95.0% C.I.for EXP(B)	
					Lower	Upper
Gender(male)	-.498	1	.536	.607	.125	2.948
Age(years)	-.026	1	.299	.974	.927	1.024
Time since of presence(year)	-.040	1	.299	.960	.890	1.036
Cigaret smoking	.161	1	.786	1.175	.367	3.755
GI symptom present	.456	1	.480	1.578	.445	5.587
Axial joint involvement	.698	1	.199	2.010	.692	5.840
High fecalcalprotectin level	1.701	1	.046	2.8	.020	4.117
CRP high	2.095	1	.001	8.123	2.290	28.819
ESR high	-.338	1	.577	.713	.217	2.343
sever As severity		2	.283			
moderateAS severity	-.740	1	.292	.477	.120	1.892
Mild AS severity	.304	1	.656	1.355	.356	5.154
Constant	-3.482	1	.128	.031		

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Discussion

The relationship between AS and IBD has been understudy in recent years. Increased gut permeability and inflammation in AS has been observed in multiple studies;however,the range of gut prevalence varies by the type of method used to assess inflammation.

We studied the prevalence of inflammatory rectosigmoid lesions and associated factors in patients with Ankylosing spondylitis by rectosigmoidoscopy. Our study showed that subclinical inflammatory lesions in the rectosigmoid mucosa are common in patients with AS.The majority of our patients (49.1%) had non-specific chronic inflammation and 15.5% suffered from inflammatory bowel disease(IBD). This was consistent with other studies including Mielants et al from Belgium (5) and a prospective study by Mielants et al in 1988. (25)
MABs against TNFα have proven efficacy in IBD and are US FDA approved to treat both IBD and AS .because this, we limited our patients study to whom previously had not used Anti TNFα.

In this study the majority of patients were male which shows the higher prevalence of this disease in men.(7) In majority of our patients,the time since diagnosis was less than five years. This could be because we excluded patients who previously had used biological medications. Cigarette smoking was not significantly related to presence of microscopic and macroscopic rectosigmoid lesions. This is in line with the preventative role of cigarettes smoking in ulcerative colitis.(7) majority of our patients were HLA B27 negative (60.9%) and there was not any significant relationship between HLA B27 status and final result of rectosigmoidoscopy and this was consistent with other studies. (25-26) We can say that negative HLA B27 in majority of our patients could be related to ethnical characteristics of the of the study area.

There was a significant relationship between CRP level and presence of microscopic and microscopic inflammatory rectosigmoid lesions which was consistent with other studies. (27,11)

Average Fecal Calprotectin level in study patients was 92.81± 40.7µgr/gr and there was a significant relationship between Fecal Calprotectin level and presence of macroscope rectosigmoid lesions which was consistent with other studies. (28,11) Based on the investigations in other studies we can say that patients with ankylosing spondylitis have high levels of Fecal Calprotectin and this is associated with rectosigmoid inflammation in this patients.

Since the choice of biological treatment in patients with ankylosing spondylitis and IBD is different and early diagnosis of subclinical inflammation in patients with AS could prevent many complications from this disease, early diagnosis of relative factors which contribute to bowel inflammation could be very helpful and effective.. We suggest that more studies including cohort and prospective studies with long-term follow-up in this group of patients could improve our understanding of contributing relative factors on inflammatory lesions. The study would more complete when a total colonoscopy could have been performed,to ensure that there were no microscopic lesions more proximally in the colon.

Conclusion

Subclinical nflammatory lesions in the rectosigmoid mucosa are common in patients with AS.older age ,more severity of As ,higher CRP level And higher fecal calprotectin are associated with rectosigmoid inflammation in this patients.

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