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Non-specific colitis among patients with colitis: frequency and relation to inflammatory bowel disease, a prospective study

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ABSTRACT

Background and study aim: The term non-specific colitis refers to an inflammatory condition of the colon that microscopically lacks the characteristic features of any specific form of colitis and is commonly seen in pathology reports of colonoscopy biopsies. In fact, it has been questioned whether it is a separate pathological entity or it is merely an intermediate stage in the course of inflammatory bowel disease. This study was conducted to estimate the prevalence of non-specific colitis among patients with colitis and characterize its natural history over a 6 months year period.

Patients and methods: Eighty adult patients presented for colonoscopy were enrolled. In the final analysis they were divided into Group A; the non-specific colitis Group and Group B; the inflammatory bowel disease Group. All patients were subjected to: full history taking, full clinical examination, laboratory investigations: which included stool analysis, CRP, ESR, complete colonoscopy and entire random colon biopsies for histopathological examination.

Results: Group A included 67 patients (83.75%) while Group B included 13 (16.25%) patients. Patients with IBD had clinical and laboratory features of inflammation significantly higher than patients with non-specific colitis. Six patients (8.95%) of non-specific colitis group developed histologic features of florid inflammatory bowel disease after 6 months. There were no independent predictors of this conversion.

Conclusion: Among our 80 patients with colonoscopy and biopsy 67 (83.75%) were diagnosed as non-specific colitis and out of them 6 patients (8.95%) were reexamined after 6 months and proved to have inflammtory bowel disese this change was not linked to predictive factors.

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Colite inespecífica entre pacientes com colite: estudo prospectivo sobre sua frequência e relação com doença inflamatória intestinal

Palavras-chave:
Colite inespecífica
Doença inflamatória intestinal
Colonoscopia
Criptite

RESUMO

Introdução e objetivos: O termo colite inespecífica (CI) refere-se a uma condição inflamatória do cólon que microscopicamente não apresenta características de qualquer forma específica de colite; é comumente observada em relatórios patológicos de biópsias de colonoscopia. De fato, tem-se questionado se esta seria uma entidade patológica separada ou apenas um estágio intermediário no curso da DII. Este estudo foi realizado para estimar a prevalência de CI entre pacientes com colite e caracterizar seu curso durante um período de seis meses.
Pacientes e métodos: O estudo incluiu 80 pacientes adultos que se apresentaram para colonoscopia. Na análise, os pacientes foram divididos em dois grupos: grupo A (CI) e grupo B (DII) Todos os pacientes foram submetidos a anamnese completa, exame clínico completo e investigações laboratoriais que incluíram análise de fezes, PCR, VHS, colonoscopia completa e biópsias aleatórias de cólon para exame histopatológico.
Resultados: Do total de pacientes, 67 foram alocados no grupo A (83,75%) e 13 (16,25%) no grupo B. Os pacientes com DII apresentavam sinais clínicos e laboratoriais de inflamação significativamente maiores do que o observado em pacientes com CI. Seis pacientes (8,95%) do grupo CI desenvolveram características histológicas de DII florida após seis meses. Não foram identificados preditores independentes para essa conversão.
Conclusão: Entre os 80 pacientes submetidos a colonoscopia e biópsia, o diagnóstico de CI foi feito em 67 (83,75%); destes, seis pacientes (8,95%) foram reexaminados após seis meses e apresentaram DII, sendo que essa conversão não foi associada a fatores preditivos.

Introduction

Inflammatory conditions of the colon is referred to as colitis and it is caused by different etiologies. However, infectious and immune colitis are the most commonly reported.[1] In the Egyptian community we do not have an accurate estimates for the prevalence rates of both. However, in our daily medical practice it is obvious that inflammatory bowel diseases (IBD) are increasing while infectious causes are decreasing particularly Bilharzial colitis due to many causes including mass screening and treatment programs together with increasing sanitary and healthy behaviors of the public.[1,2]

The term non-specific colitis (NSC) refers to an inflammatory condition of the colon that microscopically lacks the characteristic features of any specific form of colitis[3] and is commonly seen in histopathological reports following colonoscopic biopsies. In fact, it has been questioned whether it is a separate pathological entity or it is merely an intermediate stage in the course of IBD. The literature both at the local Egyptian and international levels are deficient for data concerning NSC.[3–6]

This study was conducted to estimate the prevalence of NSC among patients with colitis and characterize its natural history over a 6 months period.

Patients and methods

Study design: prospective study

Patients

This multi-center study was carried out in three Egyptian institutions. *Adult* patients presented to our endoscopy units for colonoscopy were offered to participate in the study. Patients who agreed gave a written informed consent for sharing in the study and for performing all interventions needed. Eighty patients were enrolled and were assigned according to their pathology report findings into two groups, Group A; the NSC Group and Group B; the IBD Group.

Inclusion criteria

Inclusion of patients with these criteria;

Age: above 16 years;
Any sex;
Clear indication for colonoscopy;
Good mentality to understand aim, benefits and steps of the study;
Assumed availability during the study period.

Exclusion criteria

Patients with these conditions were excluded from the study.

Cases with previous specific colitis e.g. infectious colitis, IBD, etc by history or biopsy.

Malignancy (colonic and non-colonic).

Patients with incomplete or unsatisfactory colonic examination or sampling.

Patients with prior colon surgery.

Patients with colonoscopy showed polyps, vascular ectasia or malignancy.

Patient assessment

All patients were subjected to full history taking, full clinical examination, abdominal ultrasound examination.

Laboratory investigations: included stool analysis, CRP, ESR.

Lower GIT endoscopy (complete colonoscopy) with full comment on any pathological lesions, biopsies were taken randomly from the entire colon and handled following the standard precautions and sent for the lab.

Histopathologic examination of the colonic biopsies (hematoxylin and eosin) for determining the presence of inflammatory cells including lymphocytes, plasma cells and neutrophils, ulcerated mucosa, cryptitis, crypt abscesses, etc.

Follow up: patients were not re-colonscoped except if they experienced persistence or recurrence of the symptoms

Patient management

Group A – patients with NSC were treated symptomatically.

Group B – patients with IBD were treated according to the current guidelines.

Statistical analysis

Data were checked, entered and analyzed using SPSS version 16 for data processing and statistic. Data were expressed as number and percentage for qualitative variables and mean ± standard deviation for quantitative ones. *p*-Value of <0.05 indicates significant results. Comparison between the two groups was done using *t* test, Chi square tests while paired t test was used to assess variability within the same group before and after therapy.

Ethical considerations

All patients gave a written informed consent for participating in the study and for performing all relevant interventions.

Results

Study flow

Out of 513 patients presented to our endoscopy units for colonoscopy during the study period 80 patients were included according to our inclusion criteria. Patients in the final analysis were divided into Group A ($n = 67$); are patients described by the pathologist as NSC and Group B ($n = 13$); are patients with pathologically confirmed IBD (including both UC and CD) (Fig. 1). Patients with IBD were managed following the standard practice in treatment and follow up according to the guidelines. Their mean age was 40.34 ± 10.13 years. Patients

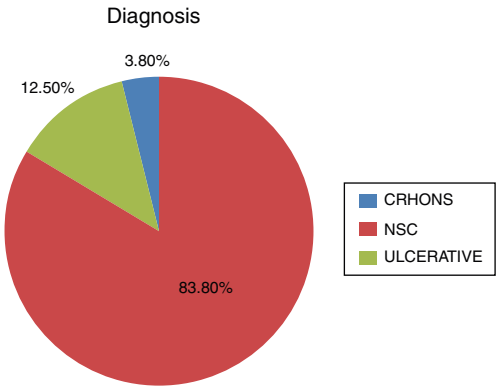

Fig. 1 – Prevalence rates of non-specific colitis among studied patients.

with NSC were given symptomatic treatments and followed up for 6 months. Patients ($n = 6$) who experienced persistent symptoms or developed new symptoms necessitating reexamination by colonoscopy and biopsy were reexamined and their data were compared to base line characteristics of other NSC patients.

Patient characteristics

There were no dropouts during the follow up. Among patients with pathologically confirmed colitis NSC represented the majority (83.75%) while IBD represented (16.25%). The demographic features of both groups are shown in Table 1 without any statistically significant difference between both groups regarding the age, sex, smoking status, education and type of diet consumed. On the other hand, laboratory findings were significantly different between both. Inflammatory activity was marked in the IBD group when compared with NSC group this is noticeable by significant detection of RBCs in the stool, positive Fecal Occult Blood (FOBT) and high CRP levels (Table 1).

Endoscopic features

The inflammatory activity noticed in the studied laboratory parameters is also reported in the endoscopic morphologic features. Patients with IBD had significantly higher rates of mucosal friability, exudates and ulcerations ($p = 0.00$) than NSC patients (Table 2).

Histopathology features

The common features of inflammation represented here as mucosal congestion and mucosal edema was not statistically different between both IBD and NSC patients. However, IBD patients had statistically significant higher rates of cryptitis, ulcers and inflammatory cell infiltrates than NSC patients. It should be obvious also that 14.9% of patients with NSC had evidence of cryptitis which means that they actually have an inflammatory activity but none of them had ulcers or granulocyte infiltration which means that they actually had quiescent chronic inflammation (Table 3).

Table 1 – Base line characteristics of both groups.

	Groups		Total	p
	NSC	Inflammatory		
Sex				0.082
Male				
n	59	9	68	
%	88.1%	69.2%	85.0%	
Female				
n	8	4	12	
%	11.9%	30.8%	15.0%	
Education				0.18
Low				
n	44	5	49	
%	64.2%	38.5%	60.0%	
Moderate				
n	20	7	27	
%	29.9%	53.8%	33.8%	
High				
n	3	1	4	
%	4.5%	7.7%	5.0%	
Smoking				0.41
No				
n	44	7	51	
%	65.7%	53.8%	63.8%	
Yes				
n	23	6	29	
%	34.3%	46.2%	36.2%	
spicy food				0.081
No				
n	21	1	22	
%	31.3%	7.7%	27.5%	
Yes				
n	46	12	58	
%	68.7%	92.3%	72.5%	
Stool				0.0004[b]
Loose				
n	41	3	42	
%	61.2%	23.1%	55.0%	
Nil				
n	12	1	13	
%	17.9%	7.7%	16.2%	
Pus				
n	4	0	4	
%	6.0%	0.0%	5.0%	
RBCs				
n	10	9	19	
%	14.9%	69.2%	23.8%	
Occult blood				0.005[*]
−VE				
n	27	0	27	
%	40.3%	0.0%	33.8%	
+VE				
n	40	13	53	
%	59.7%	100.0%	66.2%	
CRP				0.001[b]
−VE				
n	52	4	56	
%	77.6%	30.8%	70.0%	
+VE				
n	15	9	24	
%	22.4%	69.2%	30.0%	

NSC; non-specific colitis; IBD, inflammatory bowel disease; +VE, positive; −VE, negative; CRP, C-reactive protein.

[a] Significant.

[b] Highly significant.

Table 2 – Colonoscopy features of both groups.

	Groups		Total	p-Value[a]
	NSC (*n* = 67)	IBD (*n* = 13)		
Friability				0.00[**]
−VE				
n	58	1	59	
%	86.6%	7.7%	73.8%	
+VE				
n	9	12	21	
%	13.4%	92.3%	26.2%	
Exudate				0.00[b]
−VE				
n	57	4	61	
%	85.1%	30.8%	76.2%	
+VE				
n	10	9	19	
%	14.9%	69.2%	23.8%	
Ulcer				0.00[b]
−VE				
n	55	1	56	
%	82.1%	7.7%	70.0%	
+VE				
n	12	12	24	
%	17.9%	92.3%	30.0%	

NSC, non-specific colitis; IBD, inflammatory bowel disease; +VE, positive; −VE, negative; CRP, C-reactive protein.

[a] Significant.

[b] Highly significant.

Follow up of NSC patients

Follow up of patients with NSC for a 6 months period showed that 6 patients out of the 67 (8.95%) re-examined again by colonoscopy and biopsy due to persistence of symptoms *and had confirmed evidence of IBD* and their new pathology had confirmed an evidence of florid IBD. When the 6 patients compared with the remaining 61 NSC patients it is obvious that the converted patients at base line when compared with other NSC patients had significant inflammatory features including loose motions containing pus and RBSs, high CRP levels and on endoscopy showed mucosal friability, exudates while in pathology they had significant higher mucosal edema and cryptitis. While occult blood, mucosal congestion and granulocytes infiltration was not significantly different between both groups (Table 4).

Table 3 – Pathologic features in both groups.

	Groups		Total ($n=80$)	p-Value[a]
	NSC ($n=67$)	IBD ($n=67$)		
Cryptic				0.00[b]
−VE				
n	57	3	60	
%	85.1%	23.1%	75.0%	
+VE				
n	10	10	20	
%	14.9%	76.9%	25.0%	
Crypt ulcer				0.00[b]
−VE				
n	67	3	70	
%	100.0%	23.1%	87.5%	
+VE				
n	0	10	10	
%	0.0%	76.9%	12.5%	
Mucosal congestion				0.087
−VE				
n	27	2	29	
%	40.3%	15.4%	36.2%	
+VE				
n	40	11	51	
%	59.7%	84.6%	63.8%	
Edema				0.77
−VE				
n	49	9	58	
%	73.1%	69.2%	72.5%	
+VE				
n	18	4	22	
%	26.9%	30.8%	27.5%	
Granulocyte				0.00[b]
−VE				
n	67	10	77	
%	100.0%	76.9%	96.2%	
+VE				
n	0	3	3	
%	0.0%	23.1%	3.8%	

NSC, non-specific colitis; IBD, inflammatory bowel disease; +VE, positive; −VE, negative; CRP, C-reactive protein.
[a] Significant.
[b] Highly significant.

Multivariate logistic regression showed that none of the studied parameters was an independent predictor for this conversion ($p \square 0.05$) (Table 5).

Discussion

Early in the last century the term non-specific colitis was used in describing colitis different from the common infectious colitis.[7] And nowadays it is used to describe inflammatory condition of the colon that lacks the characteristic pathologic features of the commonly known causes of colitis.[3]

In the daily practice we commonly confronted with histopathologic reports carrying the final diagnosis as NSC and at that time the commonly non-convinced physician have to convince the complaining patient about the non-fully characterized phenomenon NSC. In fact NSC as a diagnosis has long been questioned, is it a true diagnosis? What is the

Table 4 – Comparison between NSC converted to IBD and other NSC patients.

	Groups		p
	NSC ($n=61$)	NSC converted to IBD ($n=6$)	
Stool			0.00**
Loose			
n	**41**	6	
%	67.2%	100.0%	
Nil			
n	12	0	
%	19.6%	0.0%	
Pus			
n	4	6	
%	6.5%	100.0%	
RBCs			
n	4	6	
%	6.5%	100.0%	
Occult blood			0.088
−VE			
n	27	0	
%	44.3%	0.0%	
+VE			
n	34	6	
%	55.7%	100.0%	
CRP			0.00001**
−VE			
n	52	0	
%	85.3%	0.0%	
+VE			
n	9	6	
%	14.7%	100.0%	
Friability			0.0005[b]
−VE			
n	58	2	
%	91.9%	33.3%	
+VE			
n	5	4	
%	8.1%	66.7%	
Exudate			0.00[b]
−VE			
n	57	0	
%	93.5%	0.0%	
+VE			
n	4	6	
%	6.5%	100.0%	
Cryptitis			0.00[b]
−VE			
n	57	0	
%	93.5%	0.0%	
+VE			
n	4	6	
%	6.5%	100.0%	
Mucosal congestion			0.09
−VE			
n	27	0	
%	44.3%	0.0%	
+VE			
n	34	6	
%	55.7%	100.0%	
Edema			0.02*

– Table 4 (*Continued*)

	Groups		*p*
	NSC (*n* = 61)	NSC converted to IBD (*n* = 6)	
–VE			
n	47	2	
%	77.1%	33.3%	
+VE			
n	14	4	
%	22.9%	66.7%	
Granulocyte			–
–VE			
n	61	6	
%	100.0%	100.0%	
+VE			
n	0	0	
%	0.0%	0.0%	

NSC, non-specific colitis; IBD, inflammatory bowel disease; +VE, positive; –VE, negative.

* Significant.

** Highly significant.

Table 5 – Logistic multivariate regression for predictors of conversion from NSC to IBD.

Variable	95% confidence interval		OR	*p*-Value
	Lower	Upper		
Stool	0.87	87.321	4.750	0.089
CRP	0.93	17.524	2.315	0.094
Friability	0.54	5.214	1.303	0.072
Cryptitis	0.73	15.47	4.254	0.213
Edema	0.92	5.321	2.321	0.652

natural history? And what are the treatment options. And the answers for these questions can be drawn from the scares papers in the international literature.[3,5,6,8]

The first question had been raised by Haboubi and Kamal in 2001[8] and they examined a cohort of 35 patients described initially as non-specific chronic colitis and after revision of the pathology in another center the patients were as follow: 13 patients had normal histology, 7 had active inflammation, 12 patients had chronic inflammation, 2 patients had hyperplastic polyps and one patient had solitary rectal ulcer and they recommended that the term NSC should be no longer used because it gives a wrong message and is non consistent and even describes normal findings.

We agree with them in a part that inter-observer variability is there and would impact totally the yield of pathology reports. Also, we agree them in using predefined checklists for pathological findings in order to avoid including normal biopsies in this category and also we would favor examination to be done by pathologists having interest in examining colonic mucosa.

The second question had been raised by Mantzaris in 2005,[3] who concluded that the term NSC is a misnomer and better to be described as "pathology is not characteristic to a particular disease" because failure of the pathologist to categorize colonic inflammation to a particular disease is related to many factors. Factors related to the endoscopist including inadequate biopsies, timing of obtaining the biopsy in the course of inflammation and failure to supply the full clinical data of the patient to the pathologist with the biopsies given. Pathologist factors including handling and processing of the samples together with interest of the pathologist to examine the colonic mucosa. Finally factors related to the underlying disease because some disorders in their course are associated with non-characteristic colonic inflammation. The author also recommended that the disappointing NSC in pathology reports should elicit diagnostic workup searching for an underlying specific pathology.

We agree with the author because 9% of our patients who initially diagnosed as NSC were diagnosed later as IBD within a short period of time. Also detailed history taking points to high prevalence of IBS among NSC patients.

The last question is a clinical dilemma and usually raised not only by clinicians but more often by patients. And it seems hard to answer particularly when the patients are complaining. Consequently, some authors[4] proposed that NSC is an acceptable diagnosis when clinical data are lacking, and the presence of NSC should trigger more diagnostic work up[3] to elicit diagnosis. Because many disorders in their course had dense chronic inflammatory cell infiltrate in the colonic mucosa e.g. diverticular disease, IBS, NSAID colitis, bile salt malabsorption and resolving infectious colitis.[3,4]

There is some sort of agreement in the literature that NSC is not a separate disease entity.[3–6,8] One study showed that even cases with normal colonic mucosa (37% of studied patients) have been initially diagnosed as NSC before the pathology was revised.[8] In another study with 104 patients followed for 3 years 54% were later diagnosed as ulcerative colitis, 33% with *Crohn's disease* and 13% remained unclassified and the authors suggested that NSC could potentially be undiagnosed IBD.[6]

The clinical significance of NSC was questioned in one study[5] which included retrospectively 101 patients with their biopsy reports showed NSC with median follow up of 5 years, 50.5% of patients had at least one subsequent colonoscopy and 19 out of 101 patients with nonspecific colitis biopsies were treated for IBD due to persistent symptoms suggestive of IBD (18.8%), and 6 out of the 19 patients had subsequent biopsies showing IBD.

When our findings in this study are compared with previous studies some stops are figured out. First stop, our study was prospective in comparison to retrospective nature of others. Second stop, we followed our patients for shorter duration of 6 months in comparison to 3–5 years in the other studies[5,6] because we do not have electronic database for our patients. Third stop, we reexamined by colonoscopy and biopsy only 6 patients (8.95%) depending on persistence of symptoms when compared with reexamination rate of 50.5% in the study of Tsang and Lo Savio.[5] Because patients are not usually compliant with colonoscopic examination. Furthermore, we did not treat patients for IBD without histological confirmation. The prevalence rates of IBD in our cohort with NSC over 6 months period is approximately 9% figure lower than Notteghem et al.[6] and Tsang and Lo Savio[5] of 54.4% and 15.7%repectively probably due to shorter duration of follow up and lower prevalence rates of IBD in the Egyptian community when compared with their geographic regions.[2]

One important stop in this study, is the predictive factors for development of florid IBD features among NSC patients. Logistic regression analysis showed that none of the studied parameters was a predictive factor for development of IBD among those patients. The presence of chronic inflammatory cell infiltrate in the colonic mucosa as described above can be seen at some stage in the natural history of colitis due to many etiologies,[3] while cryptitis would usually suggest IBD.[9] This point in particular return the debate back to the pathologist and we believe that pathologists given our clinical data should had reported these patient as IBD from the early beginning. Hereby, we agree with most of the authors[3–6,8] that NSC should not overlook our work up for underlying specific pathology and we advise clinicians to analyze pathological reports hand in hand with patients' clinical information mainly history taking, clinical examination and endoscopic features.

In conclusion, among our 80 patients with colonoscopy and biopsy 67 (83.75%) were diagnosed as NSC which is a quiet high prevalence rate and out of them 6 patients (8.95%) were reexamined after 6 months and proved to have IBD.

Conflicts of interest

The authors declare no conflicts of interest.

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REFERENCES

1. Salama RI, Emara MH, Amer I, Elsharawy S. Prevalence of amebiasis among histologically confirmed colitis patients. J Gastroenterol Hepatol Res. 2018;7:2604–8.
2. Esmat S, El Nady M, Elfekki M, Elsherif Y, Naga M. Epidemiological and clinical characteristics of inflammatory bowel diseases in Cairo, Egypt. World J Gastroenterol. 2014;20:814–82.
3. Mantzaris GJ. What is the natural history of a patient with "non-specific" colitis on large bowel histology? Ann Gastroenterol. 2005;18:116–8.
4. Geboes K, Villanacci V. Terminology for the diagnosis of colitis. J Clin Pathol. 2005;58:1133–4.
5. Tsang RW, Lo Savio A. Clinical significance of nonspecific colitis. Gastroenterology. 2013;144:S1: S-438.
6. Notteghem B, Salomez JL, Gower-Rousseau C, Marti R, Lemahieu M, Nuttens MC, et al. What is the prognosis in unclassified colitis? Results of a cohort study of 104 patients in the Northern-Pas-de-Calais region. Gastroenterol Clin Biol. 1993;17:811–5.
7. Hare DC. Therapeutic observations on non-specific colitis: (section of therapeutics and pharmacology). Proc R Soc Med. 1935;29:19–30.
8. Haboubi NY, Kamal F. Non-specific colitis, is it a justifiable diagnosis? Colorectal Dis. 2001;3:263–5.
9. DeRoche TC, Xiao SY, Liu X. Histological evaluation in ulcerative colitis. Gastroenterol Rep (Oxf). 2014;2:178–92.