Gastroenterology & Hepatology Letters

MINI-REVIEW

Non-specific Colitis: An Endoscopist-Pathologist Miscommunication

Mohamed H. Emara[1]*, Eman M. Saied[2], Mohammed Hussien Ahmed[1], Yasmin A. Elshaer[1]

[1]Department of Hepatology, Gastroenterology and Infectious Diseases, Faculty of Medicine, Kafrelsheikh University, Kafr Elshiekh, Egypt
[2]Department of Pathology, Faculty of Medicine, Kafrelsheikh University, Kafr Elshiekh, Egypt

Abstract: Pathologists commonly report non-specific colitis (NSC) in the pathology reports of colon biopsies when they fail to characterize features of the colonic inflammation and diagnose the disease based on specific forms of colitis. Several conditions, ranging from irritable bowel syndrome, diverticular disease, celiac disease, to other systemic diseases have been proposed to be associated with the reporting of NSC in the colon pathology reports. Specifically, NSC could be a preceding pathological condition associated with these diseases before their symptoms and signs become more apparent. Based on a few studies, NSC may not be a particular disease, but rather a transient presentation of inflammatory bowel disease. This gist of this mini-review article is the failure of sharing demographic, clinical, laboratory, and endoscopic data between endoscopist and pathologist are the most important underlying cause of failed characterization of colitis by pathologists. Therefore, enhancement of endoscopist-pathologist communication would reduce the incidence of this misnomer and indirectly improve the diagnosis that helps with more accurate treatment.

Keywords: Pathology, Non-specific colitis, Irritable bowel syndrome, Inflammatory bowel disease, Colonoscopy

Received: July 21, 2020
Accepted: September 17, 2020
Published Online: October 14, 2020

***CORRESPONDING AUTHOR**
Dr. Mohamed H. Emara,
Email: emara_20007@yahoo.com

CITATION
Emara MH, Saied EM, Ahmed MH, Elshaer YA, 2020, Non-specific Colitis: An Endoscopist-Pathologist Miscommunication. *Gastroenterol Hepatol Lett*, 2(1):17-22.
DOI: 10.18063/ghl.v2i1.254

1 Background

Inflammation of the colon is referred to as "colitis" and there is an extending list of causes that vary from infectious colitis, inflammatory bowel disease (IBD), to drug- or radiation-induced colitis[1,2]. Non-specific colitis (NSC) is a common finding registered in the pathology reports of colon biopsies. This finding is relatively a disappointing and confusing diagnostic test result because the clinicians always find themselves in a difficult situation to convince the patient about the nature of colonic inflammation. It is important to recognize that both endoscopist and pathologist who are specialized in gastrointestinal pathology play important roles in the diagnosis of colitis.

From the pathologist's point of view, NSC is characterized by colonic mucosal inflammation that lacks pathognomonic features of a specific disease, particularly the inflammatory cells infiltrate (Figure 1) or morphological changes of the glands or epithelium[3]. The inflammation of colonic mucosa may be acute or chronic based on the findings regarding the types of inflammatory cells present; the infiltration of mucosa with lymphocytes, plasma cells, and macrophages is a typical characteristic of chronic inflammation, while the presence of polymorphs is the hallmark of active inflammation[3].

A good understanding of the normal architecture of the colonic mucosa helps pathologists make more accurate diagnosis. The mucosa of the colon consists of crypts arranged in tubular forms that are perpendicular to the muscularis mucosa. The distance

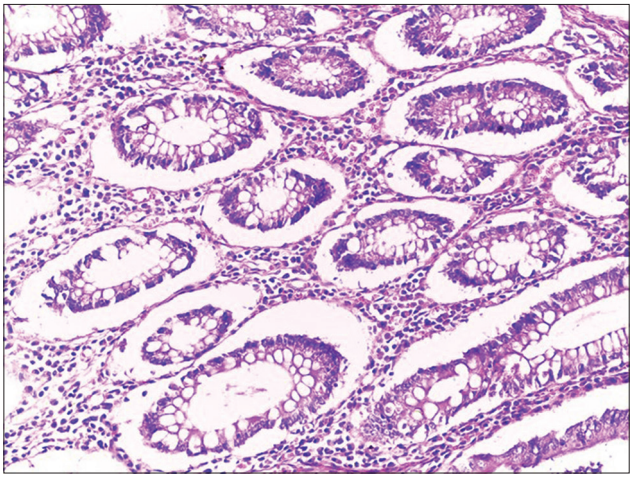


Figure 1. Colonic mucosal biopsy specimen with normal gland architecture and mucosal infiltration by chronic inflammatory cells.

between the crypts and the internal diameter of the crypts is constant. Despite that, a slight variation in crypt architecture, inter-cryptal spacing, and occasional crypt branching may occur. The epithelium lining the crypts consists of a higher proportion of goblet cells interspersed among the absorptive cells compared to that of the small intestine. The lamina propria that surrounds the crypts normally contains eosinophils, lymphocytes, plasma cells, and a few histiocytes. The right colon, in contrast to left colon, contains more cells in lamina propria and higher density of cells, especially plasma cells and eosinophils. The cells in the right colon are higher and closer to ileocecal valve. The normal rectum mucosa has fewer inflammatory cells in the lamina propria compared to the right colon and more goblet cells on the surface of the mucosa[4]. With a good grasp of colonic mucosa architecture, clinicians would know which part of the colon should be biopsied for diagnostic purposes, and the pathologists would make well-informed decision based on the pathological findings covering aspects such as the cellularity of colonic mucosa.

Although the suggestion that regard NSC as a transient presentation of IBD has been gaining traction, this condition is still registered as a common pathological finding in pathology reports of colon biopsies when pathologists fail to characterize features of colonic inflammation. According to published literature, we opine that the term non-specific colitis or NSC is a potential misnomer, and it should not be the major finding of a pathological report as this could hinder or delay the accurate diagnosis. In this mini-review, the possible causes of this misnomer phenomenon and natural history of NSC are discussed with emphasis on published literature.

2 Possible causes of the misnomer phenomenon

The misnomer phenomenon of NSC facing the clinicians is possibly attributed to the miscommunication between the endoscopist and pathologist. In addition, the diseases in colon with non-specific histologic features of the colonic mucosa represent another trigger of the misnomer phenomenon, particularly when the communication between endoscopist and pathologist is compromised while finalizing the pathology report.

Several authors believed that irritable bowel syndrome (IBS) is probably the most common cause of the misnomer phenomenon of NSC[3]. This is because IBS is a gastrointestinal disorder characterized by chronic abdominal pain or discomfort in association with colonic inflammation. Thus, there is a chance that IBS can be regarded as NSC, and such an incidence can be avoided if complete clinical data are supplied together with the pathology test request. Another disease that could be wrongly considered as NSC is diverticular disease which is characterized by the presence of small bulges or diverticula on the wall of colon, giving the incorrect impression when sampling that the colon is inflamed[5,6]. Similarly, some other conditions, including ischemic colitis, Crohn's disease, and solitary rectal ulcer syndrome, give the similar picture of apparently inflamed mucosa and non-specific histologic features[3] that potentially result in the misnomer phenomenon.

Microscopic colitis (MC) includes both lymphocytic and collagenous colitis. The hallmark of MC is watery diarrhea. The diagnosis of MC can only be established with histological means due to the absence of endoscopic or radiologic findings. MC may be wrongly interpreted as NSC if insufficient number of samples and inappropriate or incorrect regions of the colon are sampled through biopsy[3]. Furthermore, celiac disease that affects the bowel as a result of gluten sensitivity could also be wrongly regarded as NSC[7]. On the other hand, IBD that comprises two principal categories, namely, the ulcerative colitis and Crohn's disease have distinct clinical, endoscopic, and histologic features. An emerging category coined as the indeterminate colitis that lacks the characteristic features of both is not uncommonly reported in the literature. However, indeterminate colitis is frequently reported by pathologists as NSC. Some studies reported that up to 80% of patients with indeterminate colitis eventually developed characteristics of ulcerative colitis and Crohn's disease after years of follow-up[8]. In addition, celiac disease and quiescent ulcerative colitis usually manifest non-pathognomonic histologic features[3,9]. Of note, some non-disease factors, including allergies, asthma, autoimmune diseases, chronic use of laxatives, nonsteroidal anti-inflammatory drugs intake, radiation exposure, bile salt malabsorption, as well as the use of proton pump inhibitors and antibiotics, are sometimes associated with nonspecific colonic inflammation[3,9], implying their associations with the misnomer phenomenon of NSC.

The endoscopist may also be partially responsible for this phenomenon. The principal reasons that NSC, rather than other specific forms of diseases, is reported is because

inadequate specimens are biopsied from the inflamed colon, the specimen is not from the inflamed lesions, and the collected specimens are not representative of the condition[3]. The timing of biopsy relative to the course of disease is another important factor that could significantly affect the interpretation of pathologic findings. For example, if biopsy is conducted during convalescence stage of simple colitis, the findings could possibly point to NSC[3]; same results may also in resolving infectious colitis too[9]. Besides, some reports indicate that endoscopists may sample only the rectal mucosa when no obvious pathology is seen, and this was found to have been underestimating the prevalence of MC[9,10]. In some special instances, enema or the passage of endoscope induce mucosal trauma that leads to the recruitment of neutrophils to rectal mucosa, injury to the surface epithelium, disruption of mucin and blood extravasation[4], and giving the non-specific characteristics that contribute to this phenomenon.

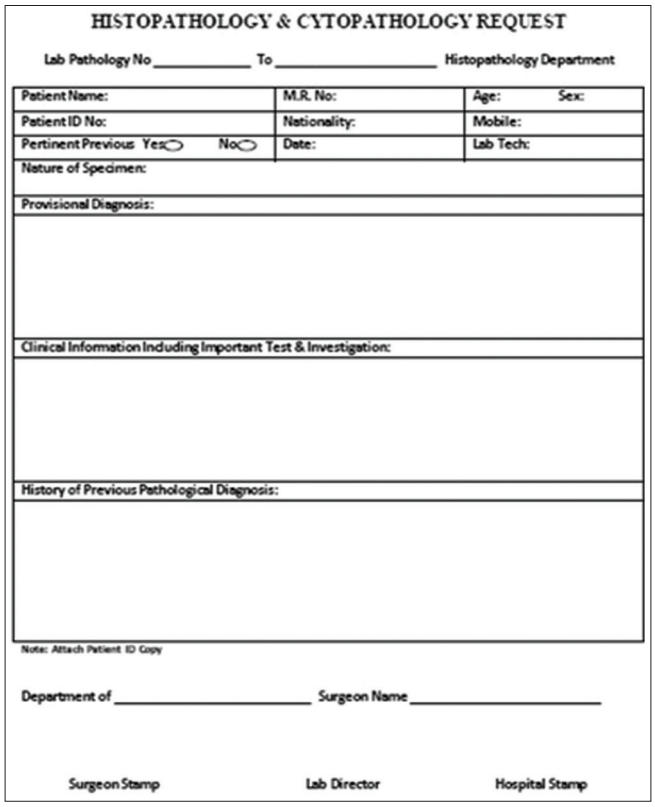
Technical failures, such as improper or inadequate processing, orientation, cutting, and staining of the histopathology specimens, usually pose serious obstacles to pathologist in assessing the histological features of colitis[3]. Experience in the interpretation of colon biopsies[3] and a huge understanding of normal architecture and cellular count for each part of the colon[4] are determining factors in assessing colitis features.

Perhaps, the most important contributing factor to this phenomenon is the lack of interaction between the endoscopist and the pathologist. The endoscopist should supply the pathologist with all patients' clinical data, including demographics, past and present clinical history, and results of clinical examination and investigations. Some centers applied a histopathology test request form that requires input of different data, including demographic (age and sex), clinical (main complain, duration of the condition, pattern of diarrhea, and drug history, allergies including food allergies, and previous colon surgeries), and endoscopic (date of colonoscopy, morphologic disease extent in different parts of the colon and terminal ileum, and sites of biopsies) data, in an attempt to reduce endoscopist-pathologist miscommunication[11]. An example of request form that does not contain more comprehensive aspect is shown in Figure 2.

3 Natural history of NSC

The natural history of NSC is not fully understood. This is due to the lack of prospective and long follow-up studies for patients with the initial diagnosis of NSC and the fact that NSC is actually is not a true diagnosis. At most, NSC is a mirror image of another condition or disease.

There are few studies in the literature focusing NSC. Seemingly, these studies deem NSC either a false diagnosis for otherwise normal colonic mucosa[12] or an initial stage in the course of other diseases. Most of the published studies agreed that NSC could turn into florid IBD in a


HISTOPATHOLOGY & CYTOPATHOLOGY REQUEST

Lab Pathology No _____ To _____ Histopathology Department

Patient Name:	M.R. No:	Age: Sex:
Patient ID No:	Nationality:	Mobile:
Pertinent Previous Yes◯ No◯	Date:	Lab Tech:
Nature of Specimen:		
Provisional Diagnosis:		
Clinical Information Including Important Test & Investigation:		
History of Previous Pathological Diagnosis:		

Note: Attach Patient ID Copy

Department of _____ Surgeon Name _____

Surgeon Stamp Lab Director Hospital Stamp

Figure 2. An example of deficient histopathology test request form. This form lacks essential clinical, endoscopic, and laboratory aspects that are supposed to reduce the endoscopist-pathologist miscommunication.

Table 1. Summarization of the findings from selected published studies focusing on NSC

Author and reference	Year	Patients	Summary of findings
Notteghem *et al.*[13]	1993	104 incidental cases of acute unclassified colitis diagnosed in 1988	• Thirteen patients were lost to follow-up. • Three patients obtained final diagnosis: Two cases of salmonellosis and one diverticulosis case. • Forty-six patients who were initially classified as having an acute unclassified colitis had relapse and were subsequently classified as having inflammatory bowel disease (54% ulcerative colitis, 33% Crohn's disease and 13% chronic unclassified colitis) after a 2.5 – 3-year-old follow-up. • Forty-two patients did not have relapse and were considered having acute NSC. • These data warrant a thorough follow-up of acute unclassified colitis, especially when it occurs in patients <40 years of age since NSC could potentially be a mirror image of IBD that is yet to be diagnosed.
Haboubi and Kamal[12]	2001	Colonic and rectal biopsies from 35 patients who presented with acute diarrhea, with an initial diagnosis of nonspecific chronic colitis	• Normal biopsies were found in 13 of the 35 patients. • Seven patients had active inflammation with no features of chronicity. • Twelve patients had active inflammation with features of chronicity. • Two patients had active inflammation with hyperplastic polyps. • One patient had active inflammation with features of solitary rectal ulcer syndrome. • The authors suggested that the inconsistent use of the term "non-specific chronic colitis" to cover a variety of conditions, including normal condition, could relay a wrong interpretation of the pathological condition; therefore, the term NSC should no longer be used.
Elbalal *et al.*[14]	2010	26 patients who had underwent colonoscopy presenting with bloody mucoid diarrhea, lower abdominal pain with or without colonic mass	This study showed that NSC has clinical features that are very much similar to mild ulcerative colitis with a rather good clinical response to oral 5-aminosalicylic acid (or mesalazine).
Tsang and Lo Savio[15]	2013	101 patients who • participated in a retrospective study with a mean follow-up period of 5.09 years • had underwent colonoscopy from January 2004 to December 2006 with biopsy outcome showing NSC • had been followed up for at least 1 year • had no previous diagnosis of a specific colitis based on history or biopsy outcome	• Approximately half of the patients subsequent colonoscopies during the follow-up period; of which, 68.6% of them present with normal condition while 15.7% had IBD. • Although self-limited colitis was most commonly reported, a portion of the patients turned out having undiagnosed IBD. • In the study, 18.8% of the patients with NSC were empirically treated for IBD-related symptoms, and 31.6% of these patients were diagnosed with IBD on subsequent colonoscopies.
Emara *et al.*[16]	2019	80 adult patients with colitis	67 patients were diagnosed with NSC; 6 of them were re-examined after 6 months and found to have IBD. The development of IBD was not associated with predictive factors.

NSC, non-specific colitis; IBD, inflammatory bowel disease

significant number of patients ranging from 9% to 54.4% over an average follow-up period of 6 months – 5 years (Table 1). All clinicians should be alerted that patients with NSC reported from their initial colon biopsy examination should be followed up to detect an underlying significant disease.

4 What is the truth?

Diagnosing an individual with NSC should not be encouraged. The truth is that the pathologist should be able to diagnose the patient based on the patient's complete medical report, including clinical history, comorbidities, clinical findings, and the relevant laboratory or radiological investigations. There should be a dialogue between the clinician and pathologist for distinguishing between different forms of colitis which is not always easy[11,17]. It is recommended that the pathologist should avoid using the term NSC when he fails to characterize the type of colitis[3,12]. Under the circumstance when a non-specific form of colitis is encountered, labeling it as "not characteristic for a particular disease" in the pathology report is generally encouraged.

The studies focusing on NSC are scarce and the most strikingly common result after re-examination or subsequent test is that NSC *per se* is a mirror image of other pathological conditions or even a misdiagnosis for the normal colonic condition. Of note, IBD is the most common disease reported after re-examination or further test. Thus, the current conundrum the clinicians and pathologists are grappling with warrants a series of studies to devise methods or biomarkers that can easily distinguish the apparent IBD cases from those with nonspecific features of colitis.

5 Conclusion

The term NSC is a misnomer used to describe a potential misdiagnosis of an underlying pathological condition of colon, mostly due to the miscommunication between the endoscopist and the pathologist. It is advisable to use different phrase "colitis not characteristic for a particular disease" in pathology reports to avoid misunderstanding that could lead to inaccurate decision in making a diagnosis and subsequent treatment planning.

Acknowledgments

The authors would like to thank all colleagues who helped in the preparation of this review.

Conflict of interest

All authors declare that they do not have any conflict of interest regarding this article.

Author contributions

M.H.E and M.H.A. developed the concept of the article subject. M.H.E. and E.M.S. performed literature search. M.H.E. and Y.A.E. analyzed the retrieved literature. M.H.E. wrote the paper. E.M.S. and M.H.A. reviewed drafts of the paper. Y.A.E. verified the clarity of figures and table. All authors read and approved the final manuscript.

References

1. Salama RI, Emara MH, Amer I, *et al*., 2018, Prevalence of Amebiasis among Histologically Confirmed Colitis Patients. *J Gastroenterol Hepatol Res*, 7(3):2604–8. DOI: 10.17554/j.issn.2224-3992.2018.07.774.
2. Esmat S, El Nady M, Elfekki M, *et al*., 2014, Epidemiological and Clinical Characteristics of Inflammatory Bowel Diseases in Cairo, Egypt. *World J Gastroenterol*, 20(3):814–82. DOI: 10.3748/wjg.v20.i3.814.
3. Mantzaris GJ, 2005, What is the Natural History of a Patient with "Non-Specific" Colitis on Large Bowel Histology? *Ann Gastroenetrol*, 18(2):116–8.
4. Cerilli LA, Greenson JK, 2012, The Differential Diagnosis of Colitis in Endoscopic Biopsy Specimens: A Review Article. *Arch Pathol Lab Med*, 136:854–64. DOI: 10.5858/arpa.2012-0205-ra.
5. Cawthorn SJ, Gibbs NM, Marks CG, 1983, Segmental Colitis: A New Complication of Diverticular Disease. *Gut*, 24:500.
6. Sladen GE, Filipe MI, 1984, Is Segmental Colitis a Complication of Diverticular Disease? *Dis Colon Rectum*, 27:513–4. DOI: 10.1007/bf02555508.
7. Wolber R, Owen D, Freeman H, 1990, Colonic Lymphocytosis in Patients with Celiac Sprue. *Hum Pathol*, 21:1092–6. DOI: 10.1016/0046-8177(90)90144-t.
8. Meucci G, 2008, What is the Incidence, Prevalence, and Natural History of Indeterminate Colitis? *Inflamm Bowel Dis*, 14(2):S159–60. DOI: 10.1002/ibd.20594.
9. Geboes K, Villanacci V, 2005, Terminology for the Diagnosis of Colitis. *J Clin Pathol*, 58:1133–4.
10. Whitehead R, 1990, Mucosal Biopsy of the Gastrointestinal Tract, Other Forms of Colitis. Ch. 17. WB Saunders, Philadelphia, PA, p364.
11. Villanacci V, Manenti S, Antonelli E, *et al*., 2011, Non-IBD Colitides: Clinically Useful Histopathological Clues. *Rev Esp Enferm Dig*, 103:366–72. DOI: 10.4321/s1130-01082011000700006.
12. Haboubi NY, Kamal F, 2001, Non-Specific Colitis, is it a Justifiable Diagnosis? *Colorectal Dis*, 3(4):263–5. DOI: 10.1046/j.1463-1318.2001.00253.x.
13. Notteghem B, Salomez JL, Gower-Rousseau C, *et al*., 1993, 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*, 17(11):811–5.

14. Elbalal M, Elseed NG, Elgaili EM, *et al*., 2010, Nonspecific Colitis a Forgotten Entity in Central Sudan. *Sudan J Med Sci*, 5(4):295–8. DOI: 10.4314/sjms.v5i4.64500.
15. Tsang RW, Lo Savio A, 2013, Clinical Significance of Nonspecific Colitis. *Gastroenterology*, 144(5):S1–438.
16. Emara MH, Salama RI, Hamed EF, *et al*., 2019 Non-Specific Colitis among Patients with colitis: Frequency and Relation to Inflammatory Bowel Disease, a Prospective Study. *J Coloproctol*, 39:319–25. DOI: 10.1016/j.jcol.2019.06.004.
17. Abreu MT, Harpaz N, 2007, Diagnosis of Colitis: Making the Initial Diagnosis. *Clin Gastroenterol Hepatol*, 5(3):295–301. DOI: 10.1016/j.cgh.2006.12.032.