Journal of Crohn's and Colitis (2009) xx, xxx–xxx

available at www.sciencedirect.com

Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection

Shomron Ben-Horin [a,*], Maya Margalit [b], Peter Bossuyt [c], Jochen Maul [d], Yami Shapira [e], Daniela Bojic [f], Irit Chermesh [g], Ahmad Al-Rifai [h], Alain Schoepfer [i], Matteo Bosani [j], Matthieu Allez [k], Peter Laszlo Lakatos [l], Fabrizio Bossa [m], Alexander Eser [n], Tommaso Stefanelli [o], Franck Carbonnel [p], Konstantinos Katsanos [q], Davide Checchin [r], Inés Sáenz de Miera [s], Walter Reinisch [n], Yehuda Chowers [g], Gordon William Moran [t]
for the European Crohn's and Colitis Organization (ECCO)

[a] *Sheba Medical Center, Tel-Aviv University, Israel*
[b] *Hadassah Medical Center, Hebrew University, Jerusalem, Israel*
[c] *University of Leuven Hospitals, Leuven, Belgium*
[d] *Medizinische Klinik I, Campus Benjamin Franklin, Charité-Universitätsmedizin, Berlin, Germany*
[e] *Tel-Aviv Medical Center, Tel-Aviv, Israel*
[f] *Zvezdara University Medical Center, Belgrade, Serbia*
[g] *Rambam Medical Center, The Technion, Haifa, Israel*
[h] *Salford NHS University Hospital, Manchester, United Kingdom*
[i] *University Hospital of Bern, Switzerland*
[j] *Sacco University Hospital, Milan, Italy*
[k] *Saint-Louis Hospital, Paris, France*
[l] *Semmelweis University, Budapest, Hungary*
[m] *Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy*
[n] *Medical University of Vienna, Austria*
[o] *Fondazione IRCCS Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, UO Gastroenterologia, Università degli Studi di Milano, Italy*
[p] *University hospital of Besançon, France*
[q] *University Hospital of Ioannina, Greece*
[r] *University of Padua, Italy*
[s] *Hospital General Yagüe, Burgos, Spain*
[t] *University of Birmingham, United Kingdom*

* Corresponding author. Gastroenterology Department, Sheba Medical Center, Tel Hashomer 52621, Israel. Tel.: +972 3 5302694; fax: +972 3 5303160.
E-mail address: sben-horin@013.net.il (S. Ben-Horin).

1873-9946/$ - see front matter
doi:10.1016/j.crohns.2009.11.001

Please cite this article as: Ben-Horin S, et al, Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection, J Crohn's Colitis (2009), doi:10.1016/j.crohns.2009.11.001

Received 1 October 2009; received in revised form 31 October 2009; accepted 1 November 2009

KEYWORDS
Inflammatory bowel disease;
Clostridium difficile;
Infection

Abstract

Background and aim: Limited data suggests that pseudomembranes are uncommon in patients with inflammatory bowel disease (IBD) and *C. difficile* associated disease (CDAD), but the reason for this is unknown.
We aimed to evaluate the rate of pseudomembranes in this population, identify predictive factors for pseudomembranes' presence and assess its clinical impact.
Methods: This was a sub-study of a retrospective European Crohn's & Colitis Organization (ECCO) multi-center study on the outcome of hospitalized IBD patients with *C. difficile*. The present study included only patients who underwent lower endoscopy during hospitalization, and compared demographic and clinical parameters in the group of patients with discernable pseudomembranes versus those without.
Results: Out of 155 patients in the original cohort, 93 patients underwent lower endoscopy and constituted the study population. Endoscopic pseudomembranes were found in 12 (13%) of these patients. Patients with pseudomembranes presented more commonly with fever ($p=0.02$) compared to patients without pseudomembranes. No difference between the two groups was found with respect to the use of immunosuppressant drugs, background demographics or disease characteristics. Neither was there a difference between the group with or without pseudomembranes in the frequency of severe adverse clinical outcome or in the duration of hospitalization. On multi-variate analysis the presence of fever remained independently associated with the finding of pseudomembranes (OR 6, 95% CI 1.2–32, $p=0.03$).
Conclusions: This study documents that hospitalized IBD patients with CDAD have low rate of endoscopic pseudomembranes, which is not accounted for by the use of immunosuppressant drugs. IBD patients with CDAD and discernable pseudomembranes more commonly present with fever, but their clinical outcome is similar to patients without pseudomembranes.

1. Introduction and background

The incidence and severity of *Clostridium difficile* associated disease (CDAD) among patients with inflammatory bowel disease (IBD) is greater than its rate in the non-IBD population,[1,2] and the incidence is increasing in recent years.[3,4] Clinical guidelines have therefore advocated the early diagnosis and treatment of CDAD in flaring IBD patients.[5]

CDAD in the IBD population may manifest differently than in other population, making its symptoms indistinguishable from an exacerbation of IBD. For instance, bloody diarrhea is commonly present in cases of CDAD in IBD whereas loose watery diarrhea is the hallmark of CDAD in other populations.[6–8] Moreover, recent evidence suggest that up to 8% of IBD patients in remission harbor colonizing toxicogenic *C. difficile*, [9] thereby casting some doubt on the diagnostic interpretation of a positive toxin assay in this unique population. In addition to these diagnostic caveats, anecdotal reports suggest that pseudomembranes may be less common among IBD patients with CDAD compared to other populations. However, this has not been well documented. Moreover, there are no studies pertaining to the clinical significance of the absence or presence of pseudomembranes in IBD patients.

Thus, the present study aimed to investigate the frequency of pseudomembranes among patients with IBD and CDAD. A secondary aim was to explore clinical predictors for the occurrence of pseudomembranes and to elucidate their clinical impact.

2. Methods

2.1. Study design and population

This was a sub-study of a European Crohn's & Colitis Organization (ECCO) multi-center retrospective study previously reported elsewhere.[6] The source study encompassed all patients hospitalized with a co-diagnosis of IBD and concomitant CDAD from 1st January 2000 to 1st March 2008 in the participating centers. Details on the methods of cases identification and definition of treatment can be found in the original report.[6] In the present study, a sub-analysis was performed only for patients who underwent lower endoscopy during their hospitalization and in whom the presence or absence of endoscopic pseudomembranes was recorded. The presence of pseudomembranes was defined by the original report written by the performing endoscopist at each center. Patients were divided into a group with pseudomembranes and a group without, and the two groups were compared for the use of immunosuppressant drugs, demographic and clinical parameters, as well as the clinical outcome of hospitalization. The main clinical outcome investigated was a composite outcome comprised of the following parameters: mortality or colectomy within 3 months of admission with CDAD-IBD (in-hospital or after discharge), colon perforation or megacolon during hospitalization, shock (defined by the need for intravenous vasopressive support), or the need for mechanical ventilation. Additional clinical outcomes compared between the groups with and without

Please cite this article as: Ben-Horin S, et al, Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection, J Crohn's Colitis (2009), doi:10.1016/j.crohns.2009.11.001

pseudomembranes were the duration of hospitalization, the need to substitute antibiotics due to CDAD persistence and CDAD relapse—defined as re-hospitalization within 3 months with an admission diagnosis of CDI.

The study was approved centrally by the ethics committee of the Sheba Medical Center, and was also approved or exempted locally by the respective ethics committee at each of the participating centers.

2.2. Statistical analysis

Continuous variables were analyzed by two-tailed Student *t*-test or Mann–Whitney *U*-test, as appropriate, and categorical variables were analyzed by Fisher Exact test. Correlations were tested by Spearman's rank correlation test. Variables differing between groups with a significance level of $P<0.15$ were then entered into multi-variate analysis model consisting of a multiple backward logistic regression to identify factors independently affecting dichotomous clinical outcomes. All statistics were performed using MedCalc software (Mariakerke, Belgium). $P<0.05$ was considered significant.

3. Results

Out of the 155 patients of the original study, who were hospitalized with IBD and CDAD in the 20 participating centers in Europe and Israel, 93 (60%) underwent lower endoscopy. These patients comprised the study population. Endoscopic pseudomembranes were detected in 12 (13%) of these patients, coming from 7 centers (4 patients with pseudomembranes were found in a single center at Belgrade out of the 8 patients endoscoped at that site). In 77 (83%) of the total 93 patients, biopsies were obtained and available. Histological pseudomembranes were found in 3 specimens. In one of these 3 patients, microscopic pseudomembranes were reported in the absence of macroscopically discernable pseudomembranes at endoscopy. In 90 out of 93 patients, the diagnosis was made by positive toxin enzyme immunoassay. One patient was diagnosed by positive *C. difficile* culture (culture was positive in additional 8 patients who had also positive toxin assay). Two patients were diagnosed solely by histological documentation of pseudomembranes.

The clinical characteristics of the study cohort, stratified according to the presence or absence of endoscopic pseudomembranes are shown in Table 1. A similar rate of immuno-modulator drugs' use was found in the two groups (Table 1), and the two groups did not differ with respect to the diagnostic procedure they underwent (i.e. colonoscopy or sigmoidoscopy). The presence of fever at the onset of disease was more common among patients with pseudomembranes compared to patients without (9/12 vs. 26/81, $P=0.02$, Fisher Exact test). Elevated leukocyte count was also more frequent in the group with pseudomembranes, but

Table 1 Background demographic and clinical characteristics.

	All patients ($n=93$)	Patients without pseudomembranes ($n=81$)	Patients with pseudomembranes ($n=12$)	*P* value
Age (years, median ± SD)	42 ± 18	43 ± 18	39 ± 15	0.5
Females	54 (58%)	49 (60%)	5 (42%)	0.3
UC	65 (70%)	57 (70%)	8 (66 %)	0.7
Mean duration of disease (years)	6.3 ± 8	6.4 ± 8	5.9 ± 6	0.6
Hospitalization in prior 3 months	24 (26%)	21 (27%)	3 (25%)	0.9
Antibiotics in prior 3 months	41 (44%)	36 (44%)	5 (42%)	0.7
PPI use in prior 3 months	13 (16%)	11 (15%)	2 (17%)	0.9
Any co-morbidities	32 (34%)	29 (36%)	3 (25%)	0.5
Admission after 2003	69 (74%)	61(76%)	8 (75%)	0.5
Any immunomodulators on admission	32 (34%)	28 (35%)	4 (33%)	0.9
Corticosteroids on admission	28 (30%)	25 (31%)	3 (25%)	0.9
Underwent colonoscopy	37 (40%)	30 (37%)	7 (58%)	0.2
Abdominal pain	59 (63%)	49 (60%)	10 (83%)	0.2
Severe diarrhea (>6 BM/day) [a]	63 (73%)	54 (73%)	9 (75%)	0.9
Fever at onset [a]	37 (42%)	26 (35%)	9 (75%)	0.02
Abdominal tenderness [a]	50 (55%)	42 (53%)	8 (66%)	0.5
Blood in stool	67 (72%)	59 (73%)	8 (75%)	0.5
Elevated Creatinine [a]	20 (23%)	19 (24%)	1 (10%)	0.4
Leukocytosis >10 k/ml	51 (55%)	42 (51%)	9 (82%)	0.1
Elevated CRP [a]	76 (92%)	65 (90%)	11 (100%)	0.6
Hb<10.5 g/dl	26 (29%)	21 (26%)	5 (42%)	0.3
Hypoalbuminemia < 3.5 mg/dl [a]	49 (62%)	41 (60 [a])	8 (80%)	0.3
Mean duration of hospitalization (days)	17 ± 14	17 ± 15	15 ± 10	0.8
Relapse	13 (14%)	10 (12%)	3 (25%)	0.3
C. difficile treatment failure	11 (12%)	8 (10%)	3 (25%)	0.15
Adverse outcome	9 (10%)	9 (11%)	0 (0%)	0.6

The *p* values represent the comparison between the group with and without pseudomembranes
[a] Percentages are calculated out of the patients with available data.

Please cite this article as: Ben-Horin S, et al, Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection, J Crohn's Colitis (2009), doi:10.1016/j.crohns.2009.11.001

Table 2 Multi-variate analysis by backward logistic regression showing the odds ratio for occurrence of pseudomembranes for parameters found on uni-variate analysis to correlate with this finding with a significance level of $P \leq 0.15$.

Parameter	Odds ratio	Confidence interval	*P* value
Fever at onset	6.2	1.2–32	0.03
Leukocytosis >10 k/ml	3	0.6–15	0.2
C. difficile treatment failure	2.7	0.5–14	0.24

this difference did not reach statistical significance (Table 1). Importantly, there was no difference in the clinical outcome of the two groups with respect to death or colectomy within 3 months of hospitalization, occurrence of megacolon, perforation or hemodynamic shock. Neither was the presence or absence of pseudomembranes associated with prolongation of the hospitalization, nor with higher rate of *C. difficile* persistence or relapse (Table 1). Next, a multi-variate analysis was performed to define whether parameters that correlated with the presence of pseudomembranes in the uni-variate analysis were independently associated with this endoscopic finding. The results of the multi-variate analysis are shown in Table 2 and show that fever remained associated with appearance of pseudomembranes.

4. Discussion

The present study examined the prevalence and clinical correlates of pseudomembranes in IBD patients found to be inflicted with CDAD.

Previous case-series anecdotally alluded to the rarity of pseudomembranes in IBD population inflicted by *C. difficile*.[10,11] In one single-center study, no pseudomembranes were detected in any of the 16 CDAD-IBD patients who underwent lower endoscopy, although no details on the specific Endoscopy performed (sigmoidoscopy or colonoscopy) were provided.[12] The present study comprises the largest number of endoscoped IBD patients with *C. difficile* to date, and documents that endoscopic pseudomembranes are seldom found in this population. It is known that in up to one third of patients with CDAD, pseudomembranes may be present only in the right colon and may therefore be missed by a sigmoidoscopic examination.[7,13] Indeed, 7/37 (19%) of the patients who underwent full colonoscopy had pseudomembranes compared to only 5/56 (9%) of those who underwent only a sigmoidoscopic examination; thereby suggesting the true incidence of pseudomembranes in IBD patients may be somewhat higher. However, this difference did not reach statistical significance, and even the higher rate of 19% is still lower than the 50–60% rate of endoscopically-visible pseudomembranes in reference populations.[14,15] It should be noted however, that not all patients with CDAD in the general population have pseudomembranes, as some may have endoscopic non-specific findings which correspond to grade 1 lesions on histology.[16] Thus, caution should be employed when comparing pseudomembranes rate across populations. Nevertheless, as far as endoscopically-visible lesions are concerned, the validity of our observation is further supported by its derivation from procedures performed by large number of endoscopists from different hospitals across Europe. This is likely to reduce the probability of a false negative finding due to any individual endoscopist awareness or judgment.

Why then are pseudomembranes rare in IBD patients with *C. difficile*? One possibility is that the cases with pseudomembranes colitis are diluted by the high rate of *C. difficile* asymptomatic carriage among IBD patients.[9] As noted, it is also possible that some patients have histo-pathological lesions of lesser degree that are not detected by endoscopy.[16] Yet another explanation has been proposed by a recent study reporting that concomitant immunosuppression prevents the development of pseudomembranes.[11] Whilst this is an attractive hypothesis, it was forwarded based on endoscopic findings in only 4 IBD and 4 stem cell transplanted patients who were all taking immunomodulators. The present larger-scale study, encompassing patients with and without concomitant immunomodulators, could not corroborate that it is the concomitant immunosuppression that predisposes to the absence of pseudomembranes. Other background factors, such as a younger age (IBD patients with CDAD may be younger than the general population with CDAD) or prior exposure to hospitalization and/or antibiotics were also not predictive of the risk to develop pseudomembranes. The only factor associated with the occurrence of pseudomembranes was fever at presentation. This association, which may possibly be present also in the general CDAD population, is intriguing as it may suggest a more systemic inflammatory reaction in the pseudomembranes cases. Conversely, it may otherwise point to different dominant cytokine pathways in patients with or without pseudomembranes. For instance, Il-6-dependent pathways which also propagate fever could be hypothesized to play a more dominant mechanistic role in patients with pseudomembranes, although the similar elevations of CRP among the two groups argue against this postulation. Thus, more data is needed in order to elucidate this observed correlation between fever at presentation and the development of pseudomembranes and to investigate its pathogenic implications.

The present study also addressed the question whether the occurrence of pseudomembranes signifies a more severe disease or an adverse outcome. This may be important prognostic tool for early initiation of aggressive therapy for high risk sub-groups. However, patients with pseudomembranes have not fared worst in clinical outcomes of death, colectomy, relapse of CDAD, or the duration of hospitalization.

Several limitations of this study need to be acknowledged. Fever was the only parameter differing between the two groups, but the relative limited number of patients in the pseudomembranes group ($n=12$) may possibly blunt other dissimilarities. Another limitation is the fact that 4 out of 12 patients with pseudomembranes came from a single center, thereby possibly causing some skewing of the results. However, taking out those patients from the analysis would in fact strengthen the main finding of this study, namely, that pseudomembranes are rare among IBD patients with CDAD. Thus, this limitation probably does not affect the main message of this work.

In conclusion, endoscopically-visible pseudomembranes are seldom present in patients with CDAD-associated IBD exacerbation. The reason for this is unclear, but is not related to

Please cite this article as: Ben-Horin S, et al, Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection, J Crohn's Colitis (2009), doi:10.1016/j.crohns.2009.11.001

increased immuno-suppressor drug use in this population. The presence of pseudomembranes is associated with fever on presentation, but is otherwise of little impact on the clinical course or its outcome. Clinicians should be wary of ruling out CDAD in IBD patients based on the absence of pseudomembranes.

Acknowledgments

This study was made possible through the support of Y-ECCO and ECCO.

Shomron Ben-Horin conceived the study and drafted the manuscript. Maya Margalit, Peter Bossuyt, Jochen Maul, Yami Shapira, Daniela Bojic, Irit Chermesh, Ahmad Al-Rifai, Alain Schoepfer, Matteo Bosani, Matthieu Allez, Peter Laszlo Lakatos, Fabrizio Bossa, Alexander Eser, Tommaso Stefanelli, Franck Carbonnel, Konstantinos Katsanos, Davide Checchin, Inés Sáenz de Miera, Walter Reinisch, Yehuda Chowers, and Gordon Moran have all participated in acquisition of data, analysis of data and critical revision of the manuscript for important intellectual content.

References

1. Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;**5**:339–44.
2. Nguyen GC, Kaplan GG, Harris ML, et al. A national survey of the prevalence and impact of *Clostridium difficile* infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;**103**:1443–50.
3. Bossuyt P, Verhaegen J, Van Assche G, Rutgeerts P, Vermeire S. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. *JCC* 2009;**3**:4–7.
4. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalization burden associated with *Clostridium difficile* in patients with Inflammatory Bowel Disease. *Gut* 2008;**57**:205–10.
5. Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *JCC* 2009;**3**:47–91.
6. Ben-Horin S, Margalit M, Bossuyt P, Maul J, Shapira Y, Bojic D, et al. Moran GW; For The European Crohn's And Colitis Organization (ECCO). *Clin Gastroenterol Hepatol* 2009;**7**:981–7.
7. Hookman P, Barkin JS. *Clostridium difficile* associated infection, diarrhea and colitis. *World J Gastroenterol* 2009;**15**:1554–80.
8. Pascarella F, Martinelli M, Miele E, Del Pezzo M, Roscetto E, Staiano A. Impact of *Clostridium difficile* infection on pediatric inflammatory bowel disease. *J Pediatr* 2009;**154**:854–8.
9. Clayton EM, Rea MC, Shanahan F, Quigley EM, Kiely B, Hill C, et al. The vexed relationship between *Clostridium difficile* and inflammatory bowel disease: an assessment of carriage in an outpatient setting among patients in remission. *Am J Gastroenterol* 2009;**104**:1162–9.
10. Greenfield C, Aguilar Ramirez JR, Pounder RE, Williams T, Danvers M, Marper SR, et al. *Clostridium difficile* and inflammatory bowel disease. *Gut* 1983;**24**:713–7.
11. Nomura K, Fujimoto Y, Yamashita M, Morimoto Y, Ohshiro M, Sato K, et al. Absence of pseudomembranes in *Clostridium difficile*-associated diarrhea in patients using immunosuppression agents. *Scand J Gastroenterol* 2009;**44**:74–8.
12. Issa M, Vijayapal A, Graham MB, et al. Impact of *Clostridium difficile* on inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;**5**:345–51.
13. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis* 2008;**46**(Suppl 1):S12–18.
14. Kelly CP, LaMont JT. *Clostridium difficile* infection. *Annu Rev Med* 1998;**49**:375–90.
15. Gerding DN, Olson MM, Peterson LR, Teasley DG, Gebhard RL, Schwartz ML, et al. *Clostridium difficile*-associated diarrhea and colitis in adults. A prospective case-controlled epidemiologic study. *Arch Intern Med* 1986;**146**:95–100.
16. Price AB, Davies DR. Pseudomembranous colitis. *J Clin Pathol* 1977;**30**:1–12.

Please cite this article as: Ben-Horin S, et al, Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and *Clostridium difficile* infection, J Crohn's Colitis (2009), doi:10.1016/j.crohns.2009.11.001