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Case Report

Is there a Connection between Inflammatory Bowel Disease Exacerbation, *Clostridium difficile* Infection and Thrombocytosis?

Abstract

Aim: To show if there is any connection between the activity of inflammatory bowel disease (IBD), infection with *Clostridium difficile* (*C. difficile*) and thrombocytosis in our hospitalized patients.

Methods: We performed a retrospective observational study to determine the incidence of *C. difficile* infection (CDI) and thrombocytosis in our patients with IBD hospitalized from January 1, 2007- December 31, 2012.

Results: A total of 363 hospitalized patients were identified during the observed 6-year period with a diagnosed IBD (258 patients with ulcerative colitis (UC) and 105 patients with Crohn's disease (CD). 28 (21.7%) patients with the exacerbation of UC and 17 (34.7%) patients with the exacerbation of CD were positive for CDI. Thrombocytosis was present in 65 (50.4%) patients with the exacerbation of UC and 39 (79.6%) patients with the exacerbation of CD. 26 (14.6%) patients with IBD exacerbation (15 patients with UC and 11 patients with CD) had both CDI and thrombocytosis. Statistically significant difference was found only in the incidence of thrombocytosis in patients with UC compared to patients with CD and all IBD patients.

Conclusion: We recommend testing all hospitalized IBD patients with an exacerbation for CDI because of the high prevalence of CDI in these patients and the prognostic implications of CDI in these patients. Further studies with a larger number of patients are needed to investigate the real importance of CDI and thrombocytosis in patients with IBD exacerbation and also to show if any connection between those two parameters exists.

Introduction

Inflammatory bowel diseases (IBD), that comprise ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the gastrointestinal tract of unknown aetiology. A complex interplay between the immune system, environmental factors, enteric infections, and genetic factors plays a role in the pathogenesis of IBD [1,2]. An estimated 2.5-3 million people in Europe are affected by IBD. The majority of patients experience a relapsing disease course [3]. Recent studies emphasize the importance of *Clostridium difficile* (*C. difficile*) during IBD relapse [4]. *C. difficile* is an anaerobic spore-forming Gram-positive bacillus and its toxin expression causes gastrointestinal illness with a wide spectrum of severity, ranging from mild diarrhea to pseudomembranous colitis, toxic megacolon and death [5]. A sharp rise in the rate of *C. difficile* infection (CDI) in patients with IBD has been noted in recent years and therefore higher rates of inpatient endoscopy and surgical procedures, longer length in hospital stay and higher mortality have also been reported in those patients compared to non-CDI IBD or CDI-only patients [6,7]. There have been great changes in the epidemiology of CDI in the past decade. Traditionally it was infection mostly found in the elderly, hospitalized patients, or those with a history of antibiotic exposure and today there are increasing numbers of younger and immunocompromised patients acquiring CDI [8].

Thrombocytosis is considered to be another clinical feature of IBD that is associated with the activity of disease. There is an increased incidence of systemic thromboembolism in this disease [9]. Thrombocytosis may occur under certain circumstances such as neoplastic proliferative diseases, or secondary to other conditions such as hypo- or asplenic, acute or chronic inflammation, malignant disease, blood loss or iron deficiency [10]. It is not widely accepted as a prognostic marker in patients with IBD because it can be caused by many other factors in those patients such as bowel hemorrhage or iron deficiency [11].

The aim of this retrospective study is to show the connection between CDI, thrombocytosis and activity (exacerbation) of IBD in our hospitalized patients.

Patients and Methods

We performed a retrospective observational study by using inpatient electronic medical records to determine the incidence of CDI and thrombocytosis in hospitalized IBD patients at the Department of Gastroenterology and Hepatology, Internal Medical Clinic at the Clinical Hospital "Sveti Duh" during a 6-year period from January 1, 2007- December 31, 2012. Demographic information available included age, gender and type of IBD. All hospitalized patients with diagnosed IBD were assessed for a positive fecal EIA for *C. difficile* toxin A (ImmunoCard toxins A&B; Meridian Bioscience,

Inc. USA/Corporate Office, Ohio) and for an elevated thrombocyte count ($>400 \times 10^9/L$).

Statistical analysis

Statistical analysis was done using the SAS system for Windows (rel.8.02, SAS Institute Inc., Cary, NC, SAD). Fisher's exact test was used for dependent and independent samples. Statistical significance was set at $p < 0.05$.

Results

A total of 363 hospitalized patients were identified during the observed 6-year period with a diagnosed IBD, of which 258 patients had UC and 105 patients had CD. Male to female ratio in UC was 163/95, and in CD was 49/56 with the predominance in the age groups of 20-39 and 60-79 (Table 1). 28 (21.7%) patients with the exacerbation of UC and 17 (34.7%) patients with the exacerbation of CD were positive for CDI. All *C. difficile* positive patients had negative results of stool testing for bacterial and parasitic gastrointestinal pathogens. Thrombocyte counts over $400 > 10^9/L$ were present in 65 (50.4%) patients with the exacerbation of UC and 39 (79.6%) patients with the exacerbation of CD. Also, it was noticed that the incidence of thrombocytosis was higher in patients with newly diagnosed and untreated IBD.

Statistically significant difference ($p < 0.001$) was found in the incidence of thrombocytosis in the group of patients with the exacerbation of UC compared to the group of patients with the exacerbation of CD and also compared to all patients with exacerbation of IBD. There was no statistically significant difference between other groups of patients.

26 (14.6%) patients with IBD exacerbation (15 with UC, 11 with CD) had both CDI and thrombocytosis. There was no statistically significant difference between patients diagnosed with UC and patients diagnosed with CD (Table 2).

Table 1: Characteristics of IBD patients.

PARAMETER	UC	CD
Gender:		
male	163	49
female	95	56
Age (years)	49.5+8.1	43.4+ 5.6

Table 2: Relation between IBD exacerbation, CDI and thrombocytosis.

	UC		CD		IBD (UC+CD)	
	N	%	N	%	N	%
Patients	258	100.0	105	100.0	363	100.0
Patients with exacerbation	129	50.0*	49	46.6*	178	49.0*
Patients with exacerbation and CDI	28	21.7*	17	34.7*	45	25.2*
Patients with exacerbation and thrombocytosis	65	50.4***	39	79.6**	104	58.4***
Patients with exacerbation and CDI and thrombocytosis	15	11.6*	11	22.4*	26	14.6*

*not significantly different
 ** UC/CD $p < 0.001$
 ***UC/IBD $p < 0.001$

Discussion

There is accumulating evidence that IBD results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host [12,13]. Different bacteria have been implicated in the pathogenesis of IBD, including *Mycobacterium avium paratuberculosis*, *Bacteroides fragilis*, *Escherichia coli*, *Campylobacter jejuni*, *Listeria monocytogenes*, *Chlamydia sp.*, *Aeromonas hydrophila*, *Salmonella typhi*, and *C. difficile*. However, there is no conclusive evidence that a specific pathogen is responsible for IBD onset or relapse [14-16]. The past decade has seen a dramatic change in the epidemiology of CDI which has been attributed to a new and more virulent strain BI/NAP1/027, that has also been found in patients with IBD [17,18].

IBD patients with CDI tend to be younger, have less prior antibiotic exposure, and most cases of CDI in these patients represent outpatient acquired infections. The clinical presentation of CDI in these patients can be unique and typical findings on colonoscopy are often not present [19,20]. There is an alarming increase in morbidity, mortality, need for surgery and healthcare costs resulting from *C. difficile* colitis occurring in IBD patients compared with non-infected IBD patients [19,21].

It is still not clear whether *C. difficile* is a cause of IBD or a consequence of the inflammatory state in the intestinal environment. The association between IBD and *C. difficile* may be due to different factors, such as drugs used for the treatment of IBD that might alter the intestinal flora and promote colonization, altered immune and nutritional status, frequent hospitalizations, and even genetic predisposition [22,23].

Recent studies found that 5.5%-19% of patients with the IBD exacerbation tested positive for CDI [24,25]. In our study, 25.2% of patients with the IBD exacerbation were also tested positive for CDI, and statistically significant difference between UC and CD was not found.

A growing number of studies are highlighting the importance of non-immune cells like endothelial, mesenchymal, and nerve cells, as well as platelets, in the IBD inflammatory cascade [26]. Several studies have shown that platelets represent a very important link between inflammation and coagulation in both UC and CD, creating a vicious circle in which participating parameters conserve and propagate each other [27].

The first study reporting thrombocytosis in IBD patients in 1968 by Morowitz et al. noted markedly-elevated concentration of circulating platelets during a period of increased clinical activity in a case series of IBD patients [28].

In our study, thrombocytosis was more common in patients with exacerbation of UC then in patients with exacerbation of CD or IBD, and statistically significant difference was present.

Although platelet count is correlated to IBD disease activity, it is not considered an independent risk factor for the increased risk of thromboembolic events in IBD patients [29,30]. The reported prevalence of thromboembolic events in IBD is between 1.3% and 6.0%,

with a 1.5-3.6 fold increased risk compared to the general population and other inflammatory disorders [31,32]. The development of thromboembolic events in IBD seems to be multifactorial, with interaction of genetic and acquired factors. Thromboembolic events in IBD indicate a higher predilection towards younger age compared to patients without IBD [27]. Thromboembolism is considered to be a negative prognostic outcome and represents one of the four leading causes of death in IBD patients. Thrombosis may correlate with disease activity, but it is interesting to note that one third of the events happen during clinical remission, indicating a continuous activate state of platelets and coagulation systems in IBD [33,34].

26 (14.6%) of our patients with IBD exacerbation had both CDI and thrombocytosis. We could not find any similar studies for comparison of our results.

Conclusion

Based on our results and previous experience we recommend testing all hospitalized IBD patients with an exacerbation for CDI because of the high prevalence of CDI in these patients and the prognostic implications of CDI in these patients.

There are still lacking properly designed clinical studies that would show if the connection between CDI and thrombocytosis in IBD exists. Considering that our group of patients with IBD is relatively small, further studies with a larger number of patients are needed to investigate the real importance of those two parameters in patients with IBD exacerbation.

Conflicts of Interest

The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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