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Clostridium Difficile Infection in Patients Impact Suspected Cytomegalovirus Infection in Patients with Inflammatory Bowel Disease

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ABSTRACT

Introduction: *Clostridium difficile* infection (CDI) has been reported to be a cause of flare-ups in patients with inflammatory bowel disease (IBD). Cytomegalovirus (CMV) infection can cause severe disease and complications in immunocompromised patients in consequence of disease or therapy. **Aim:** Our aim was to describe the prevalence and clinical outcomes of CDI with concomitant CMV infection in IBD patients hospitalized for flare-ups in association with the disease itself and medication used. **Methods:** We prospectively identified consecutive patients referred for CDI management during 2015-2017. Stool samples were tested for *Clostridium difficile* toxin A and/or B and Glutamate Dehydrogenase in patients with clinical symptoms. CDI patients with IBD history were tested for anti-CMV IgG and IgM antibodies by chemiluminescent microparticle immunoassay and underwent histological analysis for CMV on colon biopsies. Data were collected for demographic characteristics, treatment and outcome. **Results:** 125 patients with CDI were enrolled. Among these patients, 14 (11.2%) were diagnosed with IBD. The mean patient age of IBD patients was 52.5±15.4 years at diagnosis of CDI, 85.7% had UC, 14.3% CD, while the age of patients was shared. Eleven of the total of 14 patients (78.6%) tested positive for anti-CMV IgG. Of these, 3 patients (21.4%) exhibited high CMV IgG avidity, without detectable anti-CMV IgM and biopsy-proven CMV colitis. Of the 14 IBD patients with CDI, 8 patients (57.1%) were receiving anti-tumor necrosis factor (anti-TNF) therapy (21.4 % infliximab or golimumab, 7.1% vedolizumab or adalimumab) and 43.5% of patients were being treated with systemic corticosteroids. Four UC patients (28.6%) on steroids of the 14 CDI patients underwent a colectomy whereas none of the not on steroids patients underwent colectomy (p=0.25). Among them, 1 patient (7.1%) had recurrent CDI after 5 months from the first episode of CDI.These patients were treated with vancomycin, metronidazole and fidaxomicin. The mean age of patients that had a colectomy 65.5±9.32 (n=4) was higher than the mean age of those 47.30±14.49 (n=10) who improved ($U_{Mann-Whitney}$=6. p=0.04). **Conclusions:** Immunosuppressive medications and older age are associated with increased risk of CDI and poor outcome. Although, CMV is a rare colonic pathogen in the immunocompetent patient, it should be included and screened when exacerbation of IBD occurs in patients receiving any type of immunosuppressive therapy.

Keywords: *Clostridium difficile*, **inflammatory bowel disease, cytomegalovirus, immunosuppression, anti-TNF, infectious complications.**

1. INTRODUCTION

Inflammatory bowel disease (IBD) includes two types of idiopathic intestinal disease, ulcerative colitis (UC) and Crohn's disease (CD) that are distinguished by their location and depth of involvement in the bowel wall (1-3). The North American incidence of IBD ranges from 2.2 to 19.2 cases per 100,000 person-years for ulcerative colitis and 3.1 to 20.2 cases per 200,000 person-years for CD. IBD is much more prevalent in North America and Europe than Asia or Africa (4).

Clostridium difficile (C. difficile), a gram-positive anaerobic bacterium poses the main cause of pseudomembranous colitis (5, 6). Clostridium difficile infection (CDI) is a significant threat to the health of immunocompromised and hos-

pitalized patients. Ulcerative colitis patients are at high risk for CDI (3.7%) as well as patients with Crohn's disease (1.1%). Most clinical trials for CDI have excluded patients with underlying diarrheal disorders such as IBD, creating an evidence gap in the management of IBD patients. The impact of CDI on these populations can be notable (7).

The diagnosis of CDI is based on the detection of toxin A/B on stool or detection of toxin A/B producing C. difficile on stool by polymerase chain reaction (PCR) or culture and pseudomembrane visualization at endoscopy (8). Chronic use of antibiotics, corticosteroids and immunomodulators has been shown to increase the risk of CDI in patients with IBD (9, 10). CDI can alter the natural course of IBD, which is able to make it worsen and longer. It is neces¬sary for patients with IBD, hospitalized for flare signs and symptoms, the detection of opportunistic agents such as C. difficile and cytomegalovirus or progression of the underlying IBD as causative agent of flare (11, 12).

Corticosteroids, immunomodulators and biologic agents used in the treatment of IBD are risk factors for CDI and CMV infection (13). CDI occurrence was more frequent in IBD patients with CMV reactivation associated with poor outcomes (14). In cases of coexisting CMV and C. difficile colitis, persistent diarrhea was not due to treatment failure for C. difficile (15).In addition, a significant role of CD4 T cells in general and Th17 cells in particular during CDI identified as a potential therapeutic target for IBD patients who are at risk for severe disease (16). IBD patients are at an increased risk of developing CDI with a poorer outcome of CDI including higher rates of colectomy and death, as well as higher rates of recurrence (17-19).

Furthermore, failure to ensure the appropriate diagnosis and treatment may lead to significant morbidity and mortality (20). Although IBD is rarely reported to be associated with C. difficile and CMV co-infection studies have demonstrated disease exacerbations and poor outcomes in patients coinfected with C. difficile and CMV (21, 22).

2. AIM

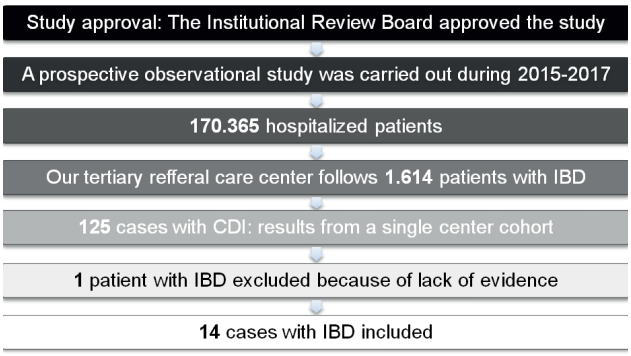
The aim of this study was to provide observational study conducted on consecutive patients referred for CDI management to our tertiary care center, University Hospital of Ioannina, Ioannina, Greece, during 2015-2017.

3. METHODS

A prospective observational study was carried out during 2015-2017 in all consecutive patients with CDI.

Stool samples were tested for C. difficile toxin A and/or B and Glutamate Dehydrogenase in patients with clinical symptoms. CDI was defined as a positive result on any of the following tests: C. difficile toxin A and/or B and Glutamate Dehydrogenase (C. diff quick check complete tox A/B+GDH; TechLab, Inc., Blacksburg, VA) and endoscopic findings, such as multiple yellowish plaques or whitish, consistent with pseudomembranous colitis.

CDI population with IBD history was tested for anti-CMV IgG and IgM antibodies by chemiluminescent microparticle immunoassay using a commercially available kit (CMIA; Abbott Laboratories, Abbott Park, IL). Additionally, these patients underwent histological analysis for CMV on colon



Flowchart of the study

biopsies. The detection of characteristic CMV inclusions was assessed in 4μm tissue sections stained with hematoxylin-eosin. Furthermore, immunohistochemical staining was performed using monoclonal Anti-Cytomegalovirus antibody (cloneDDG9+CCH2).). Data were collected for demographic characteristics, treatment and outcome.

Study sample

This study was a prospective observational study conducted on patients referred to our tertiary care center during 2015-2017. The population of the study treated in the University Gastroenterology Dept. and the 1st and 2nd Internal Medicine Dept. of the University Hospital of Ioannina, Greece. All patients who had been diagnosed with IBD based on clinical, endoscopic and histological criteria included. Patients underwent a complete diagnostic evaluation, which included detailed history and physical examination, serologic and stool tests in the presence of diarrhea. Exclusion criteria were colitis and diarrhea from

Characteristic	C. difficile infection
	(n=14)
Age (yr)	52,5±15,4
Male sex n (%)	7 (50)
Type of disease n (%)	
UC	12 (85,7)
2015	3 (21,4)
2016	1 (7,1)
2017	8 (57,1)
CD	2 (14,3)
2015	0 (0,0)
2016	1 (7,1)
2017	1 (7,1)
Medication n (%)	
Azathioprine	2 (8,7)
Mesalazine	11 (47,8)
Corticosteroids	10 (43,5)
Biologics n (%)	
Infliximab	3 (37,5)
Adalimumab	1 (12,5)
Vedolizumab	1 (12,5)
Golimumab	3 (37,5)
Recurrence rate n (%)	1 (7,1)
Colectomy rate n (%)	4 (28,6)

Table 1. Prevalence of Clostridium difficile infection, demographics and Clinical characteristics of patients with CDI

other causes, HIV/AIDS, cancer, multiple organ failure (flowchart).

Confounding Variables and factors

In this study potential confounders are conditions associated with secondary immunodeficiency as infectious agents (HIV/AIDS, Herpesvirus, human T-lymphotropic virus), drugs (chemotherapy), metabolic diseases (diabetes, renal failure, cirrhosis), malignancies (leukemia, lymphomas and solid tumors) and environmental conditions (radiation, heavy metals) as well as age.

Ethical compliance with human

The present study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration that promotes and ensures respect for all human subjects and protects their health and rights. In particular, anonymity and confidentiality of the patients were strictly observed.

Institutional review board approval

The Institutional Review Board for University Hospital of Ioannina, Greece, approved the study. No additional permissions were required to include patient data.

Statistical analysis

All statistical analyses were performed using SPSS soft¬ware version 15.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean±SD, number of cases (n) and analyzed using the non parametric test Mann-Whitney Test (small samples). Categorical variables were expressed as numbers and analyzed using the chi-square or Fisher exact test. P-values <0.05 were considered to be sig¬nificant.

4. RESULTS

During the study period, 125 patients were hospitalized because of CDI, among them; there were 14 (11,2%) patients who were diagnosed with IBD. The mean patient age of IBD patients was 52,5±15,4 years at diagnosis of CDI, 85,7% had UC, 14,3% CD, while the gender of patients was shared (50% were males and 50% were females). The prevalence, demographic and clinical characteristics of patients with CDI and IBD are summarized in Table 1.

Of the 14 patients with IBD and CDI, 8 patients (57,1%) were receiving anti-tumor necrosis factor (anti-TNF) therapy (21,4% infliximab or golimumab, 7,1% vedolizumab or adalimumab) and 43,5% of patients were being treated with systemic corticosteroids (Table 2).

Eleven of the total of 14 patients (78,6%) tested positive for anti-CMV IgG (fig. 1). Of these, 3 patients (21,4%) exhibited high CMV IgG avidity, without detectable anti-CMV IgM and biopsy-proven CMV colitis.

Four UC patients (28,6%) on steroids of the 14 IBD patients underwent a colectomy (Figure 2) whereas none of the not on steroids patients underwent colectomy (p=0.25). Among them, 1 patient (7,1%) had recurrent CDI after 5 months from the first episode of CDI. These patients were treated with vancomycin, metronidazole and fidaxomicin (Table 3). The mean age of patients that had a colectomy 65.5±9.32 (n=4) was higher than the mean age of those 47.30±14.49 (n=10) who improved (UMann-Whitney=6, p=0.04). The results of CDI suspected CMV infection in patients with IBD are summarized in Table 4.

Patient	Age/ sex	Type of disease	Medication	Antibiotics	Biologics	CMV biopsy	Outcome
1	38/F	UC	AZP	VMC, MTZ			Improved
2	68/M	UC	MSZ, CS	CPF, VMC, MTZ, MRP	IFX	-	Colectomy
3	62/M	UC	CS	VMC, MTZ, TCP, MRP		-	Colectomy
4	50/F	CD		CPF, MTZ	IFX	-	Improved
5	43/F	UC	MSZ, CS	MTZ	VDZ		Improved
6	77/F	UC	MSZ, CS	CPF, VMC	GOL	-	Colectomy
7	62F	UC	MSZ	VMC, MTZ			Improved
8	55/F	UC	MSZ, CS	CPF, MTZ, FDM	ADA	-	Colectomy
9	58/F	CD	AZP, MSZ	VMC		-	Improved
10	36/M	UC	MSZ, CS	MTZ	GOL	-	Improved
11	39/M	UC	MSZ, CS	VMC, MTZ	GOL		Improved
12	21/M	UC	MSZ, CS	FDM			Improved
13	59/M	UC	MSZ, CS	MTZ	IFX		Improved
14	68/M	UC	MSZ, CS	MTZ		-	Improved

Table 2. Patients with IBD and a Clostridium difficile infection suspected Cytomegalovirus infection. Azathioprine; MSZ, Mesalazine; CS, Corticosteroids; VMC, Vancomycin; MTZ, Metronidazole; CPF, Ciprofloxacin; MRP, Meropenem; TCP, Teicoplanin; FDM, Fidaxomicin; IFX, Infliximab; VDZ, Vedolizumab; ADA, Adalimumab; GOL, Golimumab.

Outcome	Age range (frequency) (yr) (n)	CDI in patients on steroids (n=10)	CDI in patients not on steroids (n=4)	P-value (Fisher's exact test)
Treatment n (%)				
Vancomycin	50-65 (3)	4 (28,6%)	3 (21,4%)	0.55
Metronidazole	<50 (5)	8 (57,1%)	3 (21,4%)	1.00
Fidaxomicin	>65 (2)	2 (14,3%)	0 (0,0%)	1.00
Biologics n (%)				
Infliximab	50-65, >65 (1)	2 (14,3%)	1 (7,1%)	1.00
Golimumab	<50 (2)	3 (21,4%)	0 (0,0%)	0.50
Recurrence n (%)	50-65 (1)	1 (7,1%)	0 (0,0%)	1.00
Colectomy n (%)	>50 (4)	4 (28,6%)	0 (0,0%)	0.25

Table 3. Clostridium difficile infection outcome among the study group. Values are presented as number (%), or p-value.

UC n (%)	CD n (%)	CDI n (%)	Positive anti-CMV IgG (n%)	High CMV IgG Avidity Testing n (%)	CMV biopsy negative n (%)	Steroids n (%)	Biologics n (%)	Colectomy n (%)
12 (85,7%)		12 (85,7%)	9 (64,3%)	3 (21,4%)	6 (42,8%)	10 (71,4%)	7 (50%)	4 (28,6%)
	2 (14,3%)	2 (14,3%)	2 (14,3%)		2 (14,3%)		1 (7,2%)	

Table 4. The results of CDI suspected CMV infection in patients with IBD. Values are presented as number (%).

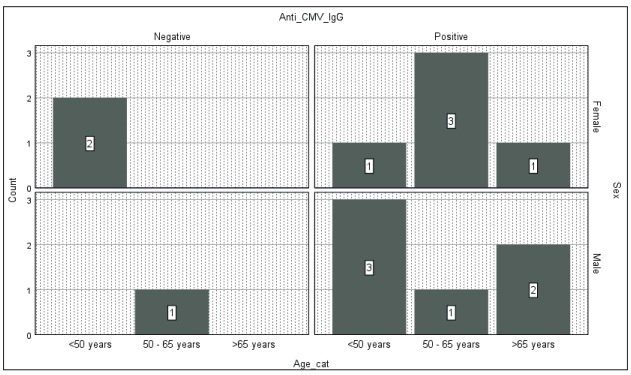


Figure 1. Patients tested for anti-CMV IgG

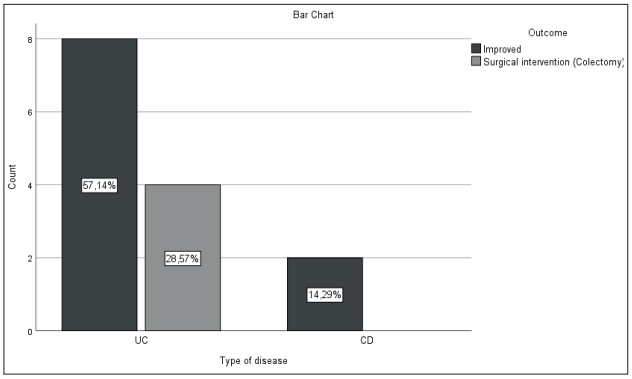


Figure 2. Clostridium difficile infection outcome

5. DISCUSSION

This study detected co-existent CDI in 14 (11,2%) IBD patients of 125 patients hospitalized with CDI. This incidence of CDI in patients with IBD is relatively high considering the incidence rate of Healthcare Associated CDI in non-IBD population (67%) (23). Our results are similar to recent studies reporting CDI incidence of 7% among hospitalized adult inpatients with IBD (24).

Furthermore, the incidence of CDI in mixed IBD populations (inpatient and outpatient) ranges between 5.1%-16.7% (25).

There is significant uncertainty among clinicians regarding the initiation of corticosteroid therapy in the setting of suspected IBD flare in a patient with known CDI. Some previous studies have reported that CDI in patients with IBD may be associated with the use of steroids describing worse outcomes among IBD patients (26, 27).

In this study of the 14 patients with CDI, 4 UC patients (28,6%) underwent a colectomy, while they were treated with corticosteroids, antibiotics and biologics (apart from one case because of suspected latent tuberculosis). However, no data exists regarding the initiation of steroid, biological (prior to CDI or after) and antibiotic therapy. Our results are in contrast with a US study reporting lack of association between the operative management and current steroids use among hospitalized patients with CDI, as well as no potential role of steroids in the treatment of CDI, although corticosteroids are a mainstay in the treatment of IBD (28).

A European study of 155 IBD patients hospitalized with CDI estimated the effects of combination antibiotic and immunomodulator therapy compared to antibiotics alone. Antibiotics and immunomodulators were associated with worse outcomes among IBD patients, higher morbidity and mortality compared to antibiotic monotherapy (29, 30).

In the setting of acute CDI in IBD patients, most recent AGA practice guidelines suggest postponing escalation of corticosteroids until 72 to 96 h after the initiation of appropriate antibiotic regimen (31). Additionally, in IBD patients with concomitant CDI, recent CDI guidelines suggest maintaining, but not escalating, existing immunosuppressive therapy, including immunomodulators such as methotrexate, azathioprine and biologic agents (32).

Also, our study highlights nonoccurrence of CMV coinfection in IBD patients with CDI and among them one (7,1%) patient with CDI recurrence had a negative CMV biopsy. Conversely, other studies revealed a higher rate of CMV coinfection in IBD patients with CDI and the association with poor outcomes (33, 34).

Furthermore, the distinguishing of CDI from CMV infection may confound the clinical picture, delaying diagnosis and following treatment, resulting in high rates of colectomy (35, 36).

Finally, IBD and the treatment strategy (often intensive, double immunosuppression) leads to an improved therapeutic success, while also increases the risk for infectious complications and especially for CDI, as well as CMV infection (37, 38). The early detection of this complication in the immunocompromised patient is often more difficult due to the similar symptoms regarding intestinal infectious complications common for a flare of the underlying disease, which is consistent with other studies (39).

Limitations of the study

The strength of this study was that consecutive patients were engaged prospectively, while microbiological tests and a wide variety of demographics and medications were included. Thus, the prevalence of CDI in hospitalized patients with IBD was quite more precise.

Nevertheless, there were several limitations to this study. First, the sample size of our population was small. Second, it is uncertain that patients with positive CDI results have CDI or are sim¬ply colonized; therefore it is difficult to distinguish between CDI and a flare of IBD.

In addition, only one academic tertiary teaching hospital participated in this study and the patients attending this hospital tend to be more severely ill than subjects from smaller hospitals. However, despite these limitations, this study shows important data on the prevalence and clinical impact of CDI suspected CMV infection in patients with IBD.

6. CONCLUSION

Immunosuppressive medications, especially when used in combination, and older age are associated with increased risk of CDI and poor outcome. This underlines the importance of adherence to guidelines for their prevention and management.

Although, CMV is a rare colonic pathogen in the immunocompetent patient, it should be included and screened when exacerbation of IBD occurs, in patients receiving any type of immunosuppressive therapy.

More data is needed on the impact that increased patho-

genic Th17 responses will have on IBD patients, targeting these cells may ameliorate IBD symptoms and reduce their risk of developing severe CDI.

- **Author's contribution:** Each author gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflict of interest:** None declared.
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