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RESEARCH ARTICLE

Association of *Clostridioides difficile* infection with specific malignant conditions

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ABSTRACT

Objectives: Patients with concomitant diseases, particularly malignancies, are at significant risk for *Clostridioides difficile* infection (CDI). However, very little is known about the association between malignancy and CDI. Therefore, we evaluated the association of CDI in patients with different kinds of malignancies compared to control patients.

Methods: Patients (n=1022) with specific malignancies (496 patients, 328 men), subgrouped as Adenocarcinoma (AC), Hematological malignancies (HM), Multiple myeloma (MM), Pediatric solid tumor (PST), and controls (526 controls, 325 men) without any specific diseases were enrolled in the study. Laboratory data of the patients were reviewed for demographics, antibiotic exposure, clinical symptoms, and fecal *Clostridioides difficile* toxin (CDT) assay.

Results: Of 1022 patients, 805 received antibiotics. CDT was positive in 168 (80.0%) of those receiving antibiotics and in 42 (20.0%) not receiving antibiotics ($p<0.001$). Bloody diarrhea was present in 12.4% with CDT status. CDI among patients with malignancy (21.2%) and controls (20.0%) was insignificant ($p=0.689$). CDT was positive in 7/25 PST (28.0%), 24/96 AC (25.0%), 71/332 HM (21.4%) and 3/43 MM (7.0%) patients, but was not significant ($p>0.05$). Correlation of different malignant conditions with control and among themselves showed male gender in AC ($p=0.039$) and HM ($p=0.003$), antibiotic exposure in MM ($p<0.001$) and fever in PST and HM subgroups to be significant ($p<0.001$).

Conclusion: CDT positivity was higher in males and patients exposed to antibiotics. No significant association of CDT was seen in malignant patients compared to the controls, though patients in PST and AC subgroups were more prone to CDI. *J Microbiol Infect Dis 2021; 11(3):124-131.*

Keywords: *Clostridioides difficile infection, Hematologic malignancy, Adenocarcinoma, Multiple myeloma, Pediatric solid tumor*

INTRODUCTION

In the last three decades, *Clostridioides difficile* infection (CDI) has become a mounting public health challenge worldwide, with a rise in the incidence in hospitalized patients. Of the several risk factors related to CDI [1], antibiotic exposure remains the foremost risk [1,2]. Among underlying conditions, malignant diseases form an essential group [3] predominantly due to prolonged hospital stay, advanced age, antibiotics, chemotherapeutic agents, and application of feeding tubes [4]. Several workers have reported that patients with solid cancers and hematologic malignancies have reduced immunity and a high risk for CDI. The gut milieu in cancer patients changes due to chemotherapy, radiotherapy, and iatrogenic processing [4]. Hospitalization rates are also reasonably high among cancer patients compared to non-cancerous populations leading to increased risk for CDI.

Data in this high-risk population regarding CDI epidemiology are sparse. Though there are

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several case reports of hospitalizations due to CDI associated with chemotherapy or antimicrobial use in patients with various cancers [5], only a few studies are available comparing CDI outbreaks among cancer patients. The first case of chemotherapy-induced CDI was reported in 1981 by Fainstein et al., [6] in a 26-year-old male with testicular embryonal cell carcinoma. This patient developed CDI with each cycle of chemotherapy but remained asymptomatic between rounds. In another study, Bilgrami et al. [7] reported 15 (7.5%) CDI among 200 patients with various malignancies after autologous peripheral blood progenitor cell transplantation. The CDI in patients undergoing chemotherapy for gynecologic cancer was reported as 2.3-7.0%, with 8.2% developing severe enterocolitis [8]. A higher risk rate for hospital-onset CDI was reported among immunocompetent cancer patients [9] and cancer patients who were immunocompromised [10] compared with non-cancer patients.

As CDI is globally rising, it becomes crucial to look for the prevalence of CDI among malignant patients. In addition, timely detection of CDI patients with concomitant malignancies may be helpful for proper clinical management of the disease. The present investigation aimed to evaluate the association of CDI in patients with specific kinds of malignancies and compare the data with control patients.

METHODS

The study is based on retrospective analysis of fecal samples referred to the division of Microbiology of the Department of Gastroenterology for testing for C. difficile toxins (CDT) by enzyme-linked immunosorbent assay (ELISA) between October 2009 and November 2016. The Institute Ethical Committee, which operates according to the Declaration of Helsinki, cleared this project (INT/IEC/2016/2599). A total of 1059 stool samples of patients with symptoms suggestive of CDI were received and included 533 samples of patients with malignancies and 526 control patients with no inflammatory bowel disease or any other known concomitant diseases. Fecal samples were subjected to C. difficile toxin A and/or B assay using ELISA kits (DRG-International Inc, USA) with positive and negative controls. An ELISA reader (Tecan Infinite F50, Austria) was used to read the results at 450 nm.

Patients' details such as age, gender, underlying disease, presence, frequency and duration of diarrhea, fever, antibiotics received, other treatments were retrieved from hospital records. Patients with malignancy were separated into (i) adenocarcinoma (AC) subgroup, (ii) hematological malignancy (HM) subgroup involving leukemia and lymphoma, (iii) multiple myeloma subgroup, and (iv) solid pediatric tumor (PST)/blastoma subgroup. Thirty-seven patients who did not fit into any of the required specific subgroups of malignancies and patients with no definitive diagnosis or those with rare tumors were excluded. So finally, there were 496 patients in the malignancy group. We do not have data on the type of treatment received for malignancy by these patients. These patients were those who were admitted for diagnosis, or for starting chemotherapy, or for surgery.

Statistical Analysis

Data analysis was carried out on R-Gui Version 3.4 statistical software. Comparative analysis of the different groups was done using Chi-square, Kruskal-Wallis, and Rank sum tests. The association of CDT distribution was tested using Chi-square statistics. Similarly, the distribution of various malignancy subgroups was also analyzed and tested. When the association was significant, stratification of the data based on patients' characteristics, antibiotic received, and clinical symptoms were done for association profiling and obtained as a percent.

RESULTS

A total of 496 patients with malignancy and 526 control patients were included in the study (Table 1). Among all 1022 patients, 210 (20.5%) tested positive for CDT; 105 for the malignancy group (21.2%) and 105 for the control groups (20.0%), but this difference was not found as significant (p=0.689). Of the total 1022 patients, 805 had received antibiotics (n=352 single; n=453 multiple). CDT positivity was 42 (20.0%) in patients who had not received any antibiotics and 168 (80.0%) in those who received antibiotics. This association was highly significant (p<0.001). Association between antibiotic receipt (p=0.026) and fever (p=0.004) in the total population was significant.

Of the 496 patients with malignancy, 274 (55.2%) had a fever, 286 (57.7%) had watery diarrhea, and 36 (7.3%) had bloody diarrhea. A total of 433 patients (87.3%) in the malignancy group and 372 (70.7%) in the control group had received antibiotics, and this association was found to be significant (p=0.026). There was no difference in the occurrence of watery diarrhea or bloody diarrhea between the malignancy patients and the controls, but a significantly higher number of patients in the malignancy group had a fever (p=0 .004).

The CDT positivity based on the number of patients receiving antibiotics, the number of patients having fever, bloody diarrhea, and watery diarrhea are given in Table 2. The association of bloody diarrhea (p=0.020) and antibiotic receipt (p<0.001) with CDT status was significant. Among 496 patients with malignancy, 332 had HM, 96 had AC, 43 had MM, and 25 had PST. Fig. 1 shows the number of CDT positivity in the controls and the different subgroups of malignancy. The number of CDT positivity differed between different malignancy subgroups. CDT was positive in 7/25 PST (28.0%), 24/96 AC (25.0%), 71/332 HM (21.4%) and 3/43 MM (7.0%) patients, but was not significant (p>0.005). The CDT positivity was 21.4% in the HM subgroup, but it was not much different from the controls.

Correlation of different malignant conditions among themselves and with controls showed male gender (p<0.001) and fever (p<0.001) to be highly significant. On comparison with controls irrespective of CDT status, male gender was significant for AC (p=0.039) and HM (p=0.003), antibiotic exposure for AC (p=0.011), HM (p<0.001) and MM (p=0.021) and fever for PST and HM (p<0.001). Fig. 2 shows the percentage of CDT positivity based on presenting features and antibiotic receipt in different subgroups of malignancy.

DISCUSSION

Malignancies are an essential risk factor for CDI precipitation because of treatment with chemotherapeutic agents, which further intensify the immunosuppressive effects of neutropenia [11-13]. In the present study, CDI among patients with malignancy and controls was insignificant. CDT was positive in 7-28.0% of various types of malignancy subgroups. Correlation of different malignant conditions with control and among themselves showed male gender and fever to be highly significant. Interestingly CDI was found to be the least (7.0%) associated with the MM subgroup compared to other subgroups in our study, even though antibiotic exposure was significantly associated.

Table 1. Demography and presenting features of all patients (n=1022).

Variables	Control (n=526)	Malignant (n=496)	p-value
Age range in years (mean ± SD)	3-103 (41±19)	0.4-86 (34.8±15.1)	NA
Gender (M)	325 (61.8%)	328 (66.1%)	0.149
Antibiotics exposure	372 (70.7%)	433 (87.3%)	0.026
Hospitalized	432 (82.1%)	471 (94.9%)	0.112
Fever	212 (40.3%)	274 (55.2%)	0 .004
Watery diarrhea	322 (61.2%)	286 (57.7%)	0.560
Bloody diarrhea	48 (9.1%)	36 (7.2%)	0.317
Frequency of diarrhea (range)	17 (14-19)	15 (13-18)	NA
Duration of diarrhea (range)	19 (15-24)	17 (13-22.5)	NA

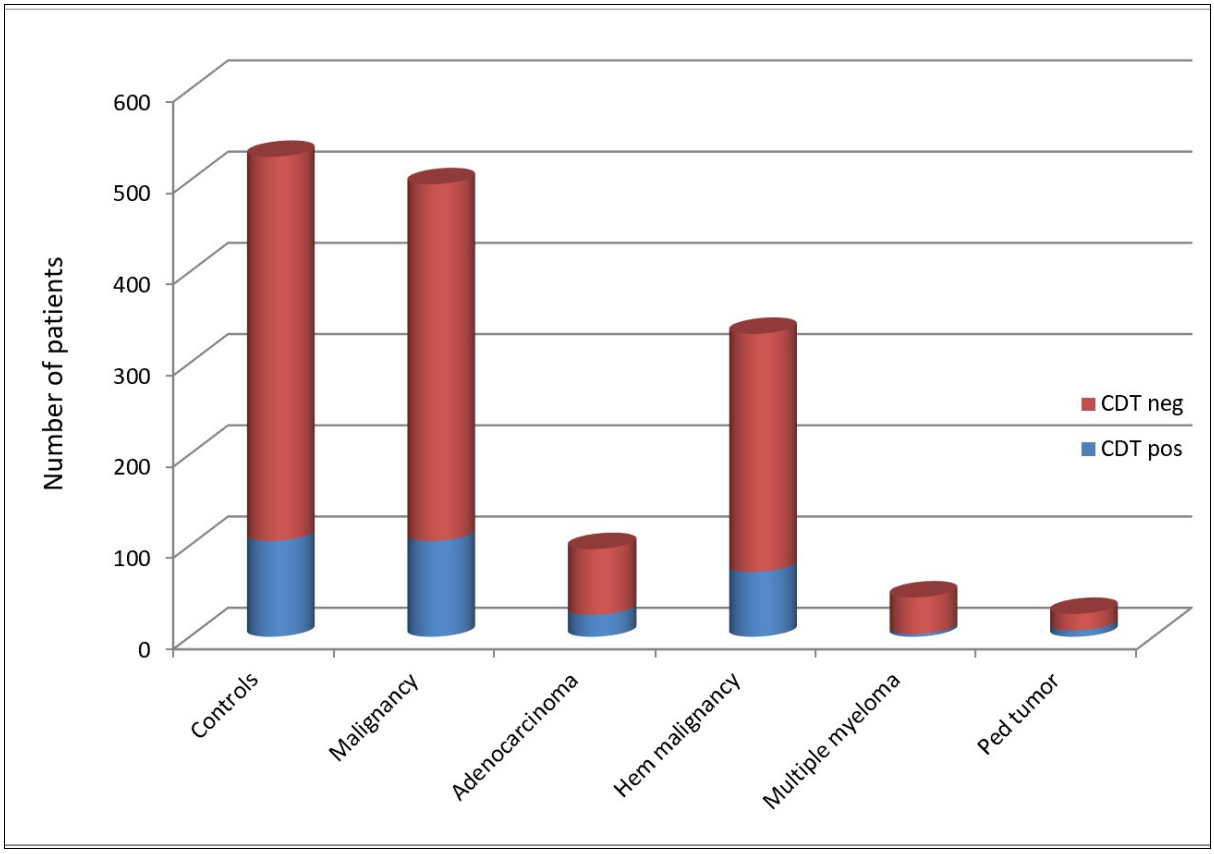

Fig. 1: Comparison of *C. difficile* toxin positivity in controls and subgroups of malignancy patients

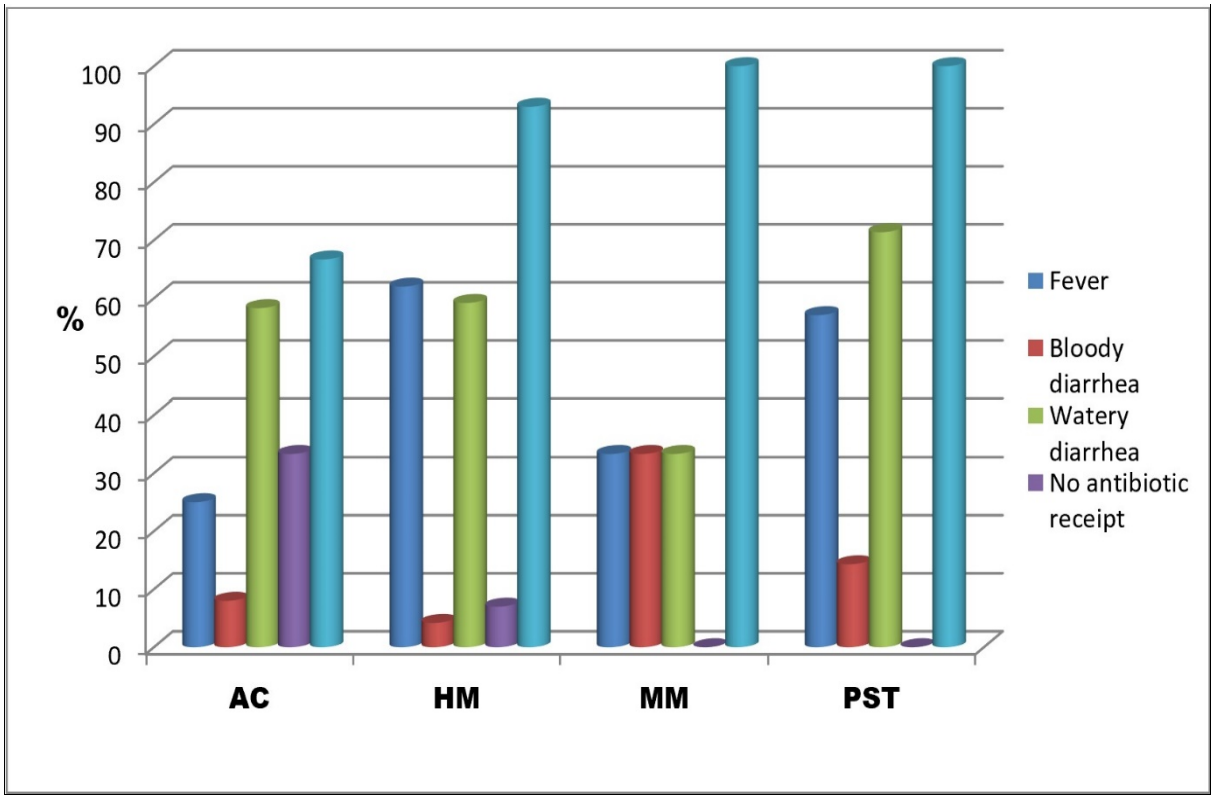

Figure 2. Presenting features and antibiotic receipt in *C. difficile* toxin positive subgroups of malignancy patients.

Table 2. Presenting features and antibiotic receipt in CDT positive malignancy and control patients.

Variables	CDT positive *n* (%)		P value
	Control (*n*=105)	Malignant (*n*=105)	
Fever	42 (40%)	54 (51.43%)	0.310
Bloody diarrhea	19 (18.09%)	7 (6.67%)	0.026
Watery diarrhea	71 (67.62%)	62 (59.05%)	0.541
No antibiotic receipt	29 (27.62%)	13 (12.38%)	0 .024
Antibiotic receipt	76 (72.38%)	92 (87.62%)	0.357

CDT=*Clostridioides difficile* toxins

In the total study population of 1022 patients, 805 received single to multiple antibiotics, and among them, 168 patients were positive for CDT. This association was, however, not found to be significant. It has been reported that cytotoxic chemotherapeutic agents can precipitate CDI even without the use of antibiotics. Yoon et al. [11] reported 19.7% CDI-related mortality in a study of 5594 adult patients with CDI receiving cancer treatment, which is greater than the 9.1–16.3% mortality reported by other workers [12-13]. Though chemotherapeutic agents are known to precipitate CDIs, there are no reports of CDI itself being induced by cancer. This has been further established by the increased risk of CDI in end-stage cancer patients who refuse chemotherapy [14].

In the present study, 526 controls comprised patients who had no malignancy of any kind, inflammatory bowel disease, or any other known concomitant diseases but were suspected of CDI clinically. Similarly, the malignancy group comprised of patients who had some malignancy, as mentioned earlier. We looked into the association of CDI with specific malignancy subgroups. Although CDT positivity was 25.0% among the AC subgroup, it was not significantly different from controls. However, the male gender was more affected, and antibiotics were more responsible for CDI precipitation. No literature is available in respect to the association of CDI with adenocarcinoma.

The CDT positivity was 21.4% in the HM subgroup, but it was different from the controls. Morris et al. [15] observed CDI in 3(6.7%) of 45 patients with various hematologic malignancies, whereas Rampling et al. [16] reported no CDI in 20 such patients, of whom 70.0% had neutropenia. Avery et al. [17] investigated 80 patients with various malignancies after autologous peripheral blood progenitor cell transplantation and reported CDI in 3 (3.8%) of them. Patients with neutropenia generally have hematologic malignancies and increased risk for developing CDI because of underlying diseases and treatment with a high dose of chemotherapeutic agents. It has been estimated that up to 7.0% of persons subjected to myelosuppressive chemotherapy for HM are likely to get CDI, with 8.2% of them developing severe enterocolitis, compared to 2.8% incidence in the general hospitalized patient groups [18]. Panichi et al. [19] reported C. difficile in 19.0% of patients with symptomatic leukemia, with most cases also having the cytotoxin. Yoon et al. [11] reported that neutropenia independently predicted CDI-related mortality. Sedhom et al. [20] investigated CDI in patients with HM and febrile neutropenia and concluded that such patients are likely to be at risk for a complex course of treatment in the hospital.

Patients with hematological malignancies may receive antibiotics due to a higher incidence of neutropenic fever ensuing from chemotherapy and have a longer length of hospital stay [21]. The use of ceftazidime antibiotic was an independent risk factor for CDI development in acute myeloid leukemia patients with hospitalization rates from 4.8% to 30.0% [22]. In contrast, Vehreschild et al. [23] reported carbapenems as the only independent risk

factor in their population of acute myeloid leukemia patients. Prince et al. [24] reported that 32.0% of treated cancer patients had a longer median duration of hospital stay than non-cancer patients due to inconsistent CDI risk factors amongst patients with blood cancer. In the present study, male gender and antibiotic exposure were the factors responsible for CDI precipitation in the HM subgroup, and clinically fever was significantly associated with CDI. From a case-control study, Lee-Tsai et al. [25] reported that though the risk factors in hematological patients developing CDI did not differ from those reported from other populations, they had an increased early mortality rate, requiring new approaches for prevention and treatment.

Interestingly CDI was found to be the least (7.0%) associated with the MM subgroup compared to other subgroups in our study. Apart from this, the presence of antibiotic receipt was found to be significantly associated with this subgroup. Unfortunately, no literature was available regarding the association of CDI with MM.

Very little literature is available regarding CDI in children with cancer. Simon et al. [26] reported a general incidence of 9.0% with a rate of 0.44 episodes/1,000 inpatient days. Apart from antimicrobial treatment, multiple hospital admissions and the presence of acute leukemia or lymphoma but not solid tumors are also identified risk factors for CDI development. Castagnola et al. [27] reported that all the drugs administered to children with cancer to treat infectious complications were related to CDI development. However, CDI was found in patients with solid tumors and not in those treated for acute leukemia, lymphoma, or in those receiving hemopoietic stem cell transplants. This was probably due to the administration of specific drugs to patients with solid tumors or because of the involvement of neutrophils in the pathophysiology of CDI. Garzotto et al. [28], in a small cohort, observed no relationship between specific types of antineoplastic therapy and CDI or between a solid tumor type and CDI.

In the present study, we found a high association of CDT positivity (28.0%) in the subgroup of patients with PST/blastoma. However, it was non-significant compared to the control group. In addition, fever was found to be a significant clinical symptom in this subgroup. Patients with localized tumors receive radiotherapy alone or a moderate simultaneous dose of chemotherapy leading to higher confined toxicity. Apart from concomitant chemotherapy, the patients generally also receive antibiotics, leading to higher precipitation of CDI.

Kamthan et al. [29] suggested that patients with severe bloody diarrhea who receive chemotherapy should be immediately tested for CDI even without any history of antibiotic receipt. However, in our study, bloody diarrhea was present in only 12.4% of patients positive for CDT and, therefore, not an essential feature of CDI.

There are some limitations to our study. The main limitation of this study is its retrospective nature. Thus, we had no access to any patients' prior treatment, including chemotherapy, radiotherapy, and surgery details. Even though we found a higher association of CDI in patients with PST/ blastomas and AC, the association was not statistically significant because of the smaller sample size in the subgroups studied. The increased CDI association in these subgroups could be because of C. difficile exposure due to recurrent or more extended hospitalizations, suppression of immunity with the disease or drug treatment, exposure to medications, and similar reasons that alter the gut microbiota. In the present study, receipt of antibiotics was an essential factor in patients with CDI. We did not find a significant association of CDI in malignant patients when compared to the control patients as reported by others as the hypervirulent strain (NAP1/BI/027) is not present in our population [30]. The strength of the present study is that the association of CDI with different kinds of malignancies has been studied for the first time. However, prospective studies should be conducted to collect more information about this with larger sample size.

Rapid diagnosis and proper CDI management are essential in patients with malignancies as a response to CDI treatment are considerably lower among patients with cancer than those without cancer. In addition, the severity of CDI in patients with hematologic malignancies may affect the choice of treatment. However, assessing the severity of CDI in cancer patients can be complicated because neutropenia is a side effect of routine

chemotherapy regimens and may complicate the choice of antibiotics.

In conclusion, CDI was not significantly associated with malignancy in our setup, though CDT was more common in patients in the PST and the AC subgroups. In addition, CDT positivity was highly associated with the male gender and in patients exposed to antibiotics.

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