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Prevalence of Intestinal Parasites in Cancer Therapy Recipients with Concurrent Diarrhea

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AAAM, AAEH and HIEN designed the study protocol. Author WAEG recruited patients and collected stool samples. Author WAEG performed the laboratory work in cooperation with authors AAAM, AAEH. All authors did literature searches. The manuscript was written by author AAEH in complete agreement with all authors who further reviewed the manuscript and approved the final draft.

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ABSTRACT

Aims: Patients receiving intensive cancer therapeutic regimens are subjected to increasing risk for developing infections including intestinal parasites. Changes in epidemiology of parasitic infections are important in those patients as some parasites may lead to prolonged and severe life threatening diarrhea. So, the purpose of the present study was to investigate the prevalence of intestinal parasites in those patients.
Study Design: This is an observational cross-sectional study.
Place and Duration of Study: Hospitalized patients in the Oncology and Radiotherapy Department, Mansoura University Hospital (MUH), Dakahlia governorate, Egypt, from December 2012 to March 2014.
Methodology: A total of 145 patients with haematological malignancy presenting with diarrhea

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while currently in the course of cancer therapy were recruited. Fresh stool samples were examined by saline, iodine mounts and after concentration with formol-ether sedimentation method. Staining of smears was performed with Trichrome, modified Trichrome, and modified Ziehl-Neelsen acid fast stains. Stool culture of fresh samples using both Harada Mori filter paper strip culture and modified agar plate was used for detection of *Strongyloides* or hookworm larvae.

Results: Intestinal parasites were detected in 124 of 145 (85.5%) subjects. *Giardia lamblia* was the most frequent parasite (36.6%), followed by *Cryptosporidium parvum* (30.3%), then *Entamoeba histolytica* (27.6%). Only *Cryptosporidium parvum* and *Entamoeba histolytica* were the parasites significantly present as mixed infections with other parasites (p= 0.006, 0.019 respectively). Persistent diarrhea was mostly associated with parasitic infections.

Conclusion: The study highlighted the importance of regular laboratory screening for intestinal parasites in patients receiving cancer therapy. Persistent diarrhea should raise high suspicion for parasitic infections in this particularly susceptible group.

Keywords: Protozoa; chemotherapy; diarrhea; immunocompromised; stool; stain.

1. INTRODUCTION

Epidemiology of infections had been changed in cancer patients owing to different chemotherapeutic regimens [1]. Cancer treatment results in impaired host immunity and neutropenia which are both significant contributing factors to the rise of infectious diarrhea [2,3].

Parasites display a wide range of pathogenicity in human, from asymptomatic infection to severe symptoms [4]. Immunosuppressed patients are highly predisposed to enteric protozoal infections with severe diarrhea and an increased risk of dissemination [5,6]. So, identification the cause of diarrhea should be urgent in this specific category as gastrointestinal infections with depressed immunity are serious and life threatening [7].

The relatively recent shift in epidemiological pattern of bacterial infection in cancer patients from Gram negative to Gram positive bacteria [8] forms a basis for investigating if the case is similar in parasitic infections. Despite their widespread prevalence, very little attention had been paid to the identification of parasitic infections in cancer therapy recipients complaining of diarrhea. So, we aimed to investigate the prevalence of intestinal parasites in this vulnerable group.

2. MATERIALS AND METHODS

2.1 Study Design

This is an observational cross-sectional study conducted on hospitalized patients in the Oncology and Radiotherapy Department, Mansoura University Hospital (MUH), Dakahlia governorate, Egypt, from December 2012 to March 2014.

2.2 Study Subjects

Inclusion criteria: Patients with underlying haematological malignancy (leukaemia or lymphoma) presenting with diarrhea while currently in the course of treatment (either chemo- or radiotherapy). Diarrhea was defined as an increase of stool frequency to three or more times a day and/or the change of stool consistency into more liquid form. Subjects were classified as having either persistent diarrhea if it lasted for more than two weeks or recurrent diarrhea if there was a history of two or more diarrhea episodes in the last six months before participating in the study [5]. Exclusion criteria: patients in remission, three months after last chemotherapy treatment, intake of antibiotics, anti-protozoal or anti-motility drugs in the preceding two weeks.

2.3 Demographic and Clinical Data

A prepared template for demographic and clinical data was filled in for each participant and all data were recorded.

2.4 Parasitological Examination

The patients were provided with wide mouthed clean, dry, properly labelled plastic containers for collection of samples. Three consecutive stool samples for each patient were examined within 1-2 hours of collection by a- Macroscopic examination for the colour, consistency, the nature of stool, presence of worms like *Ascaris lumbricoides*, *Enterobius vermicularis*, proglottids

of *Taenia saginata*, adult Hookworm and *Trichuris trichura*, either by the naked eye or with the aid of a hand lens. b- Microscopic examination*: Saline and iodine preparations* were prepared and slides were scanned for cysts and trophozoites of protozoa under low power (10×) of light microscope and confirmed under high power (40×). *Formalin ether concentration method* was performed for confirmation of positive cases or in negative cases by saline or iodine mounts. *Permanent Staining: S*mears were subjected to three staining techniques as per standard procedures; Trichrome, modified Trichrome, modified Ziehl-Neelsen acid fast stains [9] for detection of *Cryptosporidium* and microsporidia. The smears were then examined under oil immersion objective (100×) of light microscope. *Stool culture* of fresh samples was performed by both Harada Mori filter paper strip culture [10] and modified agar plate [11] for detection of *Strongyloides* or hookworm larvae.

2.5 Statistical Analysis

Descriptive statistics were calculated in the form of: Mean± standard deviation (SD), range and frequency (No-%) Analytical statistics in the form of Inter-group comparison of categorical data were performed by using chi square test (x^2-value). Data were analyzed using the computer program SPSS (Statistical package for social science) version 17.0 to obtain descriptive data. A *p* value <0.05 was considered statistically significant. And a *p* value <0.0001 was considered highly significant in all analyses.

3. RESULTS AND DISCUSSION

In the present study, 145 recipients of chemotherapy (n=124) and radiotherapy (n= 21) were recruited from Oncology center in Mansoura University Hospitals. Their mean age was 29±22.8 (range = 1-71) years. Sixty-two (42.8%) of them were males and 83 (57.2%) were females. Urban patients were 69 (47.6%), and rural patients were 76 (52.4%). Overall parasitic prevalence among studied group was 124/145 (85.5%). Fig. 1 showed the most frequently detected protozoa in stool of patients. As Table 1 implies, *Giardia lamblia* was the most frequently detected parasite (53; 36.6%) followed by *Cryptosporidium parvum* (n= 44; 30.3%) then *E. histolytica* (40; 27.6%). Most parasitic infections were present as polyparasitism rather than single infection. *E. histolytica* and *Cryptosporidium parvum* were both significantly present as mixed infections with other protozoa (p=0.019 and 0.001 respectively; Table 1). Generally, type of therapy (chemo or radiotherapy) didn't reveal a significant association with the overall prevalence of parasites although certain parasites were more common in patients receiving chemotherapy (*Giardia, E. histolytica, and* Microsporidia; Table 2).

Regarding demographic data of participants, no significant association exists between age, gender or residence and presence or absence of parasites as shown in Table 3. Finally, the association between type of diarrhea and parasitic infection revealed that acute diarrhea was significantly present in non-parasitic infected cases while persistent diarrhea was significantly associated with parasitic infections (*P* <0.001) as shown in Table 4.

Although there had been previous attempts to identify the prevalence of gastrointestinal parasites in patients with malignancy, a few of these efforts focused on those presenting with diarrhea while currently receiving treatment (chemotherapy or radiotherapy).

Table 1. Single and multiple parasitic infections in positive cases

Parasite	Single n (%)	Multiple n (%)	x^2	*P*
G. lamblia (n =53)	19 (35.8)	34 (64.2)	2.8	0.09
Entamoeba histolytica (n= 40)	11 (27.5)	29 (72.5)	5.5	*0.02
Entamoeba coli (n =16)	5 (31.3)	11 (68.8)	1.5	0.35
Blastocystis (n= 31)	15 (48.4)	16 (51.6)	0.02	0.88
H. nana (n= 2)	1 (50)	1 (50)	0	1.00
Iodamoeba bütschlii (n= 4)	0 (0)	4 (100)	2.4	0.23
C. parvum (n= 44)	11 (25)	33(75)	7.5	*0.006
Microsporidia (n= 7)	1(14.3)	6 (85.7)	2.5	0.17

**P significant at <.05*

(a) **(b)** **(c)**

Fig. 1. Microscopic photographs of the most common identified protozoa in patients stool: a) *Entamoeba histolytica* trophozoite by trichrome stain b) *Giardia lamblia* cyst by iodine stain and c) *Cryptosporidium* oocyst with modified Ziehl-Neelsen stain

In the present study, 145 recipients of chemotherapy (n=124) and radiotherapy (n= 21) were recruited from Oncology center in Mansoura University Hospitals. Parasitic prevalence among studied group was 124/145 (85.5%). Although prevalence rates ranging between (2-50%) had been previously reported among similar groups [12], our high prevalence (85%) may be due to restriction to diarrheic cases besides other contributing factors as environmental, socio-economic factors, residence, water source, food supply that may responsible for the wide variation in the prevalence of intestinal parasites [13] as well as degree of immunosuppression [14]. Our results are less than Abdel-Hafeez et al. [15] 94% among immunosuppressed children in Minia, Egypt and higher than Al-Qobati et al. [16] among patients on anticancer chemotherapy in Yemen (63.1%) but so far from Abaza and co-workers [17] who revealed a parasite prevalence rate of 23% in different groups of immunocompromised hosts and 30% by Baiomy et al. (18) in Al Azhar University Hospitals, Egypt attributed again to inclusion of only patients with diarrhea. As shown in Table (1), *Giardia lamblia* was the most frequent parasite detected (53; 36.6%), *Cryptosporidium parvum* was the 2nd most frequently detected parasite (44; 30.3%). Our results are similar to that reported by Al-Qobati et al. [16] where *Cryptosporidium parvum rate* was (30.1%) but lower than Abdel-Hafeez et al. [15]; 60.2%. No cases were found positive for *Strongyloides* by stool culture; a result that contradicts Ribes et al [19] who stated that *S. stercoralis* was frequently detected as an intestinal parasite in immunosuppressed diarrheal patients. Our results were in agreement with the studies of Baiomy et al. [18]. Also, very low prevalence rates detected by Abaza et al. [17]. Gil et al. [20] and Abdel-Hafeez et al. [15] in Egypt confirmed our results. Montes et al. [21] reported that despite all used methods, no gold standard exists for diagnosing *S. stercoralis* as patients with chronic disease have a low number of parasites and erratic larval output.

In the present study, the prevalence rates of protozoa in patients are far from rates detected in otherwise healthy individuals from Egypt e.g. Mousa et al. [22] detected a prevalence rate of 14% for *Cryptosporidium* while Ibrahim et al. [23] detected *E. histolytica* in 22.2% in Beni-Suef from Egypt, both among healthy controls with diarrhea. Also, prevalence of various protozoa was as follows among healthy individuals in another study from Egypt: *E. histolytica* 2%, *G. lamblia* 18%, *Blastocystis hominis* 10%, and *Cryptosporidium* 12% [24]. In Mansoura, results of the study conducted by Elswaif et al. [25] revealed that the prevalence of protozoa among patients attending Mansoura University Hospital out-patient clinics presenting with diarrhea was 81% for *Giardia* 15% for *Cryptosporidium* and 14% for *E. histolytica*. Finally, a recent study in Egypt comprising patients complaining of diarrhea proved that *Giardia* was the most common parasite 30.5% as detected by microscopy while *Cryptosporidium* spp. was detected in 1% of patients and *E. histolytica* in 10.8% [26] So, apart from *Giardia* which if symptomatic seems to be associated with diarrhea in Egypt [25], *Cryptosporidium parvum*, *Entamoeba histolytica* and *Blastocytis hominis* should be taken into account in patients complaining of diarrhea in the course of cancer treatment.

In the present study, most intestinal parasites exist as multiple infections and *Entamoeba histolytica* and *Cryptosporidium parvum* were both significantly present as mixed infections with other protozoa (p=0.019 and 0.001 respectively; Table 1). Polyparasitism had been recently identified as a rule rather than exception in natural infections [27]. Our results are in accordance with Büyükbaba et al. [28] where 74% of AIDS patients with diarrhea had polyparasites and Kitvatanachai et al. [29] as the rate of mixed infections (56.8%) was much higher than that of single infections (17.3%) in Thailand.

The overall parasitic prevalence was non-statistically higher in chemotherapy (86.77%), than (79.1%) in radiotherapy recipients as Table (2) implies. Although none of the parasites displayed a significant association with the type of therapy, certain species were more common in radiotherapy recipients (*Blastocystis, H. nana, Iodamoeba bütschlii* and *Cryptosporidium*); a finding that needs further exploration as radiotherapy is known to induce significant lymphopenia depending on the degree of irradiation and the site of lymphoid area involvement [30].

Table 2. Relation between parasite species and type of therapy

Parasite	Therapy				x^2	P
	Chemotherapy (n= 124)		Radiotherapy (n= 21)			
	n (%)		n (%)			
G. lamblia (n=53)	47	(37.9)	6	(28.6)	1.65	0.19
Entamoeba histolytica (n= 40)	36	(29)	4	(19)	1.7	0.19
Entamoeba coli (n=16)	14	(11.3)	2	(9.5)	0.2	0.6
Blastocystis (n=31)	23	(18.5)	8	(38.1)	2.4	0.11
H. nana (n=2)	1	(0.8)	1	(4.8)	1.6	0.2
Iodamoeba bütschlii (n=4)	2	(1.6)	2	(9.5)	3.3	0.07
Cryptosporidium (n=44)	36	(29)	8	(38)	0.12	0.7
Microsporidia (n=7)	7	(5.6)	0	(0)	1.5	0.2

Table 3. Prevalence of parasitic infection according to demographic data

Parameter		Parasite negative (n= 21)		Parasite positive (n= 124)		x^2	P
		n	(%)	n	(%)		
Gender							
	Male (n= 62)	10	(47.6)	52	(41.9)	0.24	0.6
	Female (n= 83)	11	(52.4)	72	(58.1)		
Residence							
	Urban (n= 69)	7	(33.3)	62	(50)	2.00	0.15
	Rural n= (76)	14	(66.7)	62	(50)		
Age category							
	Preschool (n= 20)	1	(4.8)	19	(15.3)	7.3	0.3
	School-age (n= 36)	5	(23.8)	31	(25.0)		
	Young adults (n= 22)	1	(4.8)	21	(16.9)		
	Adults (n= 13)	4	(19.0)	9	(7.3)		
	Middle age (n= 37)	6	(28.6)	31	(25.0)		
	Elderly (n= 17)	4	(19.0)	13	(10.5)		

Table 4. Type of diarrhea in non-infected versus infected patients

Diarrhea	Negative (n= 21)		Positive (n= 124)		x^2	P
	n	(%)	n	(%)		
Acute	6	(28.6)	2	(1.6)	25	*<0.0001
Persistent	8	(38.1)	81	(65.3)		
Recurrent	7	(33.3)	41	(33.1)		

**P significant at <.05*

Regarding type of diarrhea, acute diarrhea was strongly associated with non-parasite infected cases attributed probably to chemotherapeutic agents or radiotherapy [31], while cases with persistent diarrhea were most likely infected with parasites in accordance with Wright [32].

4. CONCLUSION

This study revealed high prevalence of protozoal infections in chemo and radiotherapy recipients presenting with persistent diarrhea especially *Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica, and Blastocystis hominis.* Regular screening and continuous monitoring of those patients should be performed to detect any possible shift in the spectrum of parasites. Future studies with larger sample sizes should be carried out so as to emphasize the results.

CONSENT AND ETHICAL APPROVAL

All authors declare that an informed consent was obtained from each patient or guardian of child and that all experiments have been examined and approved by Mansoura University ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Helsinki declaration.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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