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Opportunistic Coccidian Parasites among Saudi Cancer Patients Presenting with Diarrhea: Prevalence and Immune Status

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ABSTRACT

Cancer patients receiving chemotherapy are at risk of infection with enteric opportunistic parasites and development of chronic diarrhea which may be life-threatening. In the present study, 54 diarrheic Saudi patients receiving chemotherapy for different malignant diseases and 42 diarrheic immunocompetent attendants at King Khalid University Hospital were investigated for the coccidian pathogens: *Cryptosporidium*; *Cyclospora*, *Isospora belli*, its significance as a cause of diarrhea and its relation to CD4 T- cell count. Results showed prevalence rates of 70.3% for *Cryptosporidium* ($p < 0.001$); 51.8% for *Cyclospora* ($p < 0.001$) and 25.9% for *Isospora belli* with an overall prevalence of 88.9% among cancer patients. Higher prevalence with *Cryptosporidium* and *Cyclospora* (100 and 66.6%, respectively) were detected among patients with lymphoma. The mean CD4- T cell count among infected patients was significantly lower than that among controls. Out of 54 cancer patients, eight (14.8%) had CD4 cell count $< 200 \text{ mm}^{-3}$, all (100%) were infected with *Cryptosporidium*, 6 (75%) with *Cyclospora*, 3 (37.5%) with *Isospora belli* and 6 (75%) had mixed infections. Interpretation of results, conclusions and recommendations are presented.

Key words: *Cryptosporidium*, *Cyclospora*, *Isospora*, cancer, diarrhea, CD4 T cells, Saudi Arabia

INTRODUCTION

The immune system plays an integral part in controlling and clearing parasitic diseases. The current widespread use of immunosuppressive therapy and the growing population of individuals with immunocompromised states have altered the pattern of some parasitic infections so as they have become a major cause of global morbidity and mortality than diseases produced by any other group of organisms (Seyrafian *et al.*, 2011).

Immunosuppression as a result of chemotherapy or certain diseases has become widely spread among patients all over the world including Saudi Arabia. So, infections with opportunistic pathogens are expected to become prevalent. The opportunistic intestinal coccidians (*Cryptosporidium*; *Cyclospora* and *Isospora*) are important emerging pathogens causing diarrheal diseases. Diarrhea remains one of the most important health problems all over the world. An

estimated 1.6 to 2.5 million deaths of children under 5 years old are caused by diarrhea globally (Lopez *et al.*, 2006), with approximately 73% of these deaths being in just 15 developing countries (Boschi-Pinto *et al.*, 2007). The outcome of infection by these parasites is dependent on absolute CD4⁺ cell counts, with lower counts being associated with more severe disease, more atypical disease and a greater risk of disseminated disease. Furthermore, with immune reconstitution through effective therapy or withdrawal of immunosuppressive agents, these patients are more likely to behave like immunocompetent hosts (Sadraei *et al.*, 2005; Attili *et al.*, 2006).

Although, the opportunistic intestinal coccidian infections have a serious impact on the health of immunosuppressed patients, routine diagnosis of these diseases may be ignored during chemotherapy and their prevalence among Saudi cancer patients has not yet been studied adequately. So, the present study is meant to highlight the prevalence of the important emerging pathogens i.e., *Cryptosporidium*; *Cyclospora* and *Isospora* among Saudi cancer patients receiving chemotherapy and presenting with diarrhea and to evaluate its significance as a cause of diarrhea and its relation to CD4 T-cell count.

MATERIALS AND METHODS

A total of 54 adult patients (8 males and 46 females; 16->60 years old) presenting with diarrhea at the Oncology Unit of King Khalid University Hospital and receiving chemotherapeutic agents for different malignant diseases were included in the present study. A control group of 42 apparently immunocompetent adults presenting with diarrhea at the outpatient clinic (Ambulatory Care Services) of King Khalid University Hospital with age and sex matched with cancer patients was included. Control patients have no history of receiving specific treatment or immunosuppressive drugs.

Methodology: All patients were subjected to: (a) Full personal and medical history using structured questionnaire, present and past history of diarrhea and treatment, (b) Collection of fecal samples (at least one/patient) and microscopic examination of smears prepared from formalin-ether-fixed specimens and stained with the modified Ziehl-Neelsen staining method (Kinyoun's acid fast stain) as described by Garcia (2007), (c) Collection of blood samples and counting of CD₄-T-lymphocytes by flow cytometry (Becton Dickinson, Paramus, N.J., USA) as described by Dwivedi *et al.* (2007). This was done at the immunology lab. of King Khalid University Hospital.

Statistical analysis: Data analysis was done using the student (t) test, Chi-square test and one way ANOVA. Probability value was considered significant if p was <0.05.

The present study was carried out from October 2010 to September 2011. The study protocol was approved by the ethics review board of King Saud University (King Khalid University Hospital). Informed consent from each patient was obtained. All the tests were performed after due patient consent and in accordance with the institutional ethical guideline.

RESULTS

Prevalence of intestinal opportunistic coccidian parasites (Table 1 and 2): An overall prevalence (88.9%) of intestinal opportunistic coccidian parasites (IOCPs) among diarrheic cancer patients was detected. Forty eight out of 54 patients showed mixed coccidian infections of IOCPs. A high prevalence of 70.3% was detected for *Cryptosporidium* spp. infection followed by 51.8% for *Cyclospora* spp. with statistically highly significant difference in comparison with 17.3 and 13.04%,

Table 1: Prevalence of intestinal opportunistic coccidian parasites among diarrheic cancer patients

IOCPs	Cancer patients (n =54)		Control patients (n = 42)		Statistical analysis****
	No. +ve	(%)	No. +ve	(%)	
<i>Cryptosporidium</i> spp.	38*	70.3	8	17.30	F 32.982 P<0.001
<i>Cyclospora</i> spp.	28**	51.8	6	13.04	F 16.827 p<0.001
<i>Isospora belli</i>	14***	25.9	36	85.70	F 51.172 p<0.001

IOCPs: Intestinal opportunistic coccidian parasites, No. +ve: Positive number, *Mixed infection with *Cyclospora* spp. and *Isospora belli*, **Mixed infection with *Cryptosporidium* spp., ***Mixed infection with *Cryptosporidium* spp. and *Cyclospora* spp., ****ANOVA test

Table 2: Prevalence of intestinal coccidian parasites among diarrheic patients with different malignant diseases

Malignant disease	No. ex.	<i>Cryptosporidium</i> No. +ve (%)	<i>Cyclospora</i> No. +ve (%)	<i>Isospora</i> No. +ve (%)
Breast cancer	24	16 (61.5)	16 (61.5)	10 (38.5)
Colon cancer	12	6 (50)	2 (16.6)	0
Colon cancer with metastasis	8	8 (100)	4 (50)	0
Liver cancer	4	2 (50)	0	2 (50)
Lymphoma	6	6 (100)	4 (66.6)	2 (33.3)
Statistical analysis*		p>0.05	p<0.05	p<0.05

IOCPs: Intestinal opportunistic coccidian parasites, No. ex.: Examined No., No. +ve: Positive No., *Chi square test

respectively among the control (p<0.001). An interesting finding was the higher prevalence (85.7%) of *Isospora belli* infection among the control group in comparison with 25.9% among cancer patients.

Higher prevalence of infection with *Cryptosporidium* and *Cyclospora* was detected among patients with lymphoma (100 and 66.6%, respectively) while that with *I. belli* was higher among patients with liver cancer (50%).

Relationship between IOCPs prevalence and patient age and gender: *Cryptosporidium* infection was more prevalent (83.3%) among age group (16-40) years with insignificant difference (P > 0.05) in relation to the age groups (41-60) and (>60 years). *Cyclospora* and *Isospora* infections were more prevalent (57.1 and 28.5%, respectively) among age-group (41-60) years with insignificant difference (p>0.05) in relation to other age groups. Among the controls, no significant difference (p>0.05) was revealed between different age groups.

On the other hand, *Cryptosporidium* infection was more prevalent among males (75%) than females (69.5%) with insignificant difference (p>0.05). *Cyclospora* and *Isospora* infections were insignificantly (p>0.05) more prevalent among females (52.2 and 26.08%, respectively) in comparison to (50 and 95.23%, respectively) among males.

Relationship between CD4 T-cell count and prevalence of IOCPs (Table 3 and 4): *Cryptosporidium* infection was significantly (p<0.05) higher among patients with CD4 T cell count <500 mm⁻³ (79.69-497.03) than that among patients with CD4 T-cell count >500 mm⁻³ (532.01-1990.54). Prevalence of *Cyclospora* and *Isospora* infections was insignificantly (p>0.05) higher among patients with CD4 T-cell count <500 mm⁻³ in comparison to patients with CD4 T-cell count >500 mm⁻³.

Table 3: CD4 T-cell count among diarrheic cancer patients in relation to percentage of infection with intestinal coccidian parasites

IOCPs	Cancer patients		Statistical analysis*
	CD4 cell counts		
	<500 mm ⁻³ No. +ve (%)	≥500 mm ⁻³ No. +ve (%)	
<i>Cryptosporidium</i> spp.	18 (90)	20 (58.80)	χ ² = 5.870 p<0.050
<i>Cyclospora</i>	12 (60)	16 (47.05)	χ ² = 0.845 p>0.050
<i>Isospora belli</i>	6 (30)	8 (23.500)	χ ² = 0.270 p>0.050

IOCPs: Intestinal opportunistic coccidian parasites, No. +ve: Positive No., *Chi square test

Table 4: Relationship between CD4 T-cell count among infected cancer patients and infected control

IOCPs	CD4 cell count mm ⁻³ (Mean±SD)		Statistical analysis*
	Cancer patients	Control	
<i>Cryptosporidium</i> spp.	656.5±476.50	1493.2±650.6	t = 4.2315 p<0.0010
<i>Cyclospora</i> spp.	594.07±313.9	1351.3 ±757.5	t = 4.0493 p<0.0010
<i>Isospora belli</i>	721.8±461.30	1862.7±1147.2	t = 3.5914 p<0.0010

IOCPs: Intestinal opportunistic coccidian parasites, *Student's t-test

Table 5: Clinical status and intestinal coccidian parasitic infections among cancer patients with CD4 cell count <200 mm⁻³

Clinical status	Age (Years)	CD4 cell count<200 mm ⁻³ (n = 8)	IOCPs		
			<i>Cryptosporidium</i>	<i>Cyclospora</i>	<i>Isospora</i>
Breast cancer	50	188.27	+	+	-
Lymphoma	23	120.87	+	+	-
Colon cancer	20	79.69	+	-	-
Breast cancer	56	166.50	+	+	+
Breast cancer	47	176.47	+	+	-
Lymphoma	31	89.50	+	+	+
Colon cancer	25	110.49	+	-	-
Breast cancer	52	166.50	+	+	+

IOCPs: Intestinal opportunistic coccidian parasites, n: Number

Diarrheic cancer patients infected with *Cryptosporidium*, *Cyclospora* and *Isospora* had mean CD4 T-cell counts (Table 4) lower than those of infected controls with statistically highly significant difference (p<0.001).

Clinical status and IOCPs infections among cancer patients with CD4 count <200 mm⁻³ (Table 5): Out of 54 diarrheic cancer patients who were receiving chemotherapy, 8 (14.8%) showed CD4 count <200 mm⁻³ and 6 out of 8 (75%) had mixed infection with intestinal coccidian parasites.

Relation between percentage of infection with IOCPs, type of diarrhea and CD4 T-cell count (Table 6): Cancer patients infected with *Cryptosporidium* and presented with acute

Table 6: Intestinal coccidian parasitic infections and CD4 cell count in relation to type of diarrhea among cancer patients

IOC's	Patients				Statistical analysis
	Acute diarrhea (n = 8)		Chronic diarrhea (n = 46)		
	No. +ve (%)	CD4 count Mean±SD	No. +ve (%)	CD4 count Mean±SD	
<i>Cryptosporidium</i> spp.	8 (100)	462.2±376.6	30 (65.20)	707.8±492.5	* $\chi^2 = 3.95$, p<0.0500 **t = 1.3073, p>0.05
<i>Cyclospora</i> spp.	4 (50)	757.8±301.1	24 (52.17)	566.7±313.8	$\chi^2 = 0.0129$, p>0.05 t = 1.1323, p>0.05
<i>Isospora belli</i>	0	-	14 (30.40)	721.8±461.3	$\chi^2 = 3.29$, p>0.0500

IOCPs: Intestinal opportunistic coccidian parasites, No. +ve: Positive No., *Chi square test to compare infection rate among cancer patients with acute and chronic diarrhea, **Student "t" test to compare the mean CD4 count of cancer patients with acute and chronic diarrhea

diarrhea had a higher percentage of infection in comparison to that among those with chronic diarrhea (p<0.05). On the other hand, patients infected with *Cyclospora* and presented with acute diarrhea had an infection rate slightly lower than that among those with chronic diarrhea with insignificant difference (p>0.05). *Isospora* infection was not detected among patients with acute diarrhea while 14 out of 46 patients with chronic diarrhea had *Isospora* infection. Cancer patients presented with acute diarrhea and infected with *Cryptosporidium* had mean CD4 T-cell count insignificantly (p>0.05) lower than that in patients with chronic diarrhea. On the other hand, the mean CD4 T-cell count of *Cyclospora* infected patients with acute diarrhea (757.8±301.1) was insignificantly (p>0.05) higher than that in patients with chronic diarrhea.

DISCUSSION

The current widespread use of immunosuppressive therapy and the growing population of individuals with immunocompromised states have altered the pattern of some parasitic infections so as they have become a major cause of global morbidity and mortality than diseases produced by any other group of organisms (Seyrafian *et al.*, 2011).

Patients receiving chemotherapy for malignancy may be subjected to periods of profound immunosuppression due to both the disease condition and the treatment. In the present study, detection of parasitic infections was obtained by microscopic demonstration of parasites in smears prepared from formalin-ether-fixed specimens stained with Kinyoun's acid fast stain. Sanad and Al-Malki (2007) found that among immunocompromised patients, Kinyoun's acid fast staining was highly sensitive for detection of *Cryptosporidium* oocysts, most probably because such patients mostly present with heavy infection that can be easily identified by microscopic examination.

In the present study, the overall percentage of intestinal coccidian infection among diarrheic cancer patients was 88.9%, a finding indicates that *Cryptosporidium*, *Cyclospora* and *Isospora belli* are highly prevalent among diarrheic cancer patients in Riyadh, Saudi Arabia. The highest coccidian prevalence was 70.3% for *Cryptosporidium* followed by 51.8% for *Cyclospora* and (25.9%) for *Isospora belli* among cancer patients. Prevalence of both *Cryptosporidium* and *Cyclospora* was significantly (p<0.001) higher than among control group (17.3 and 13%, respectively). The high prevalence of all coccidians among control patients is most probably due to their being suffering from diarrhea. This emphasizes that these parasites are causative agents of diarrhea even in the immunocompetent persons. The higher prevalence of *Isospora belli* among control patients (85.7%)

in comparison with the immunocompromised patients (25.9%) was much interesting and can't be interpreted. The six diarrheic cancer patients with no coccidian parasites were found to be infected with non-coccidian intestinal parasites (Microsporidia and/or *Giardia lamblia*, *Blastocystis hominis*).

In agreement with our results, Ballal *et al.* (1999) found that (46.7%) of his immunocompromised diarrheic patients had *Cryptosporidium* oocysts. Ferreira (2000) reported that among the most important protozoa that were incriminated for causing severe diarrhea in the immunosuppressed patients were *Cryptosporidium parvum*, *Isospora belli* and *Cyclospora cayetanensis*. Similarly, Santana Ane *et al.* (2000) stated that *Cyclospora cayetanensis* is a cause of clinical disease in immunosuppressed hosts and added its relevance with prolonged, severe and highly recurrent diarrhea. Cranendonk *et al.* (2003) found that 11 and 12% of the immunocompromised patients had *C. parvum* and *I. belli* infections, respectively. Certad *et al.* (2003) found that *I. belli* accounted for upto 20% of cases of diarrhea in AIDS patients. Baqai *et al.* (2005) found that 80% of cancer patients were infected with *Cryptosporidium*. Abubakar *et al.* (2007) stated that cryptosporidiosis in the immunocompromised individuals is usually associated with chronic diarrhea and can be life threatening. Antonios *et al.* (2010) found that *Cryptosporidium* was significantly prevalent in patients with malignant diseases. Barsoum (2006) found that *Cryptosporidium* was the most common protozoon to be encountered in immunocompromised patients. Domenech *et al.* (2011) recognized *Cryptosporidium* as a cause of diarrhea associated with a high mortality in immunocompromised patients.

On the other hand, Al-Megrin (2010) reported much lower incidence (17.5%) for *Cryptosporidium* and (10.5%) for *C. cayetanensis* among immunocompromised diarrheic patients in Riyadh, Saudi Arabia. This discrepancy with our results may be due to variations in specific treatment, immunological state, type of diarrhea, date, residence, occupation and age of the patients. Similarly, contrary to our results, Guiguet *et al.* (2007) reported that immunodeficiency was shown to increase the susceptibility to infection with *Isospora belli*. Also, Baiomy *et al.* (2010) denied the presence of *Isospora belli* among immunocompromised Egyptian patients.

The high prevalence and the polyparasitism noticed in the present study among cancer patients receiving chemotherapy reflect their increased susceptibility to infection and inability to clear parasites with chronic carriage states. (Bogitsh and Cheng, 1998; Kulik *et al.*, 2008) mentioned that in those with impaired cellular immunity, killer function of macrophages is impaired, Th1 cytokine synthesis decreases and Th2 cytokine synthesis increases and differentiation of B cells and cytolytic T lymphocytes (CD8 cells) is inhibited.

In the present study, patients with lymphoma showed (100%) infection rate with *Cryptosporidium* and (66.6%) with *Cyclospora*. Those with colon cancer with metastasis also showed (100%) infection rate with *Cryptosporidium*. In agreement with our results, Evering and Weiss (2006) stated that children with acute leukemia seem to be most at risk from cryptosporidiosis. Helmy *et al.* (2006) described episodes of diarrhea associated with *C. cayetanensis* infections in patients with Hodgkin's lymphoma and acute lymphoblastic leukemia. Berenji *et al.* (2007) reported 22% incidence of cryptosporidium infection among pediatric patients with lymphohematopoietic malignancies. Domenech *et al.* (2011) described two cases of acute lymphoblastic leukemia who developed cryptosporidiosis with severe diarrhea during maintenance of chemotherapy.

In the present study, among cancer patients with CD4 T cell count $<500 \text{ mm}^{-3}$, the rates of infection with *Cryptosporidium* (90%) was significantly ($p < 0.05$) higher than that (58.8%) in patients with CD4 T-cell count $>500 \text{ mm}^{-3}$. The rates of infection with *Cyclospora* and *Isospora*

(60 and 30%, respectively) were insignificantly ($p > 0.05$) higher among patients with CD4 T-cell count $< 500 \text{ mm}^{-3}$ in comparison to patients with CD4 T-cell count $> 500 \text{ mm}^{-3}$ (47.05 and 23.5%, respectively).

These results confirm the role of CD4 T cells in the host resistance against *Cryptosporidium* infection. This is in accordance with Chen *et al.* (1993) who reported the requirements for CD4 cells in resolution of established *Cryptosporidium parvum* infection. Gassama *et al.* (2001) found that *Cryptosporidium* was often identified in patients with low CD4 counts. Kulkarni *et al.* (2009) found that half of the patients with CD4 count less than $200 \text{ cells } \mu\text{L}^{-1}$ had gastrointestinal parasitic infections and a majority of which were opportunistic parasites (37%). They added that among the opportunistic parasites, *C. parvum* (54%) was the predominant pathogen. Nearby results were reported by Wiwanitkit (2001), Sadraei *et al.* (2005) and Dwivedi *et al.* (2007).

The mean CD4 T cell count among cancer patients infected with IOCPs was significantly lower than that among the control group ($p < 0.001$). Only 8 out of 54 patients receiving chemotherapy showed CD4 T cell count $< 200 \text{ mm}^{-3}$. All were suffering from chronic diarrhea and infected with multiple coccidian parasites. This is a highlight of the controlled chemotherapy regulated upon patients attending King Khalid University Hospital.

In the present study, the number of cancer patients presented with chronic diarrhea 46 was significantly higher than that with acute diarrhea 8. All of the 8 with acute diarrhea were infected with *Cryptosporidium* (100%), 4 with *Cyclospora* and none had infection with *Isospora belli*. On the other hand, out of 46 with chronic diarrhea, 30 (65.2%) were infected with *Cryptosporidium*, 24 (52.2%) with *Cyclospora* and 14 (30.4%) with *Isospora*. In those presented with acute diarrhea and infected with *Cryptosporidium*, the mean CD4 T cell count was insignificantly ($p < 0.05$) lower than that in patients with chronic diarrhea. On the other hand, in those presented with acute diarrhea and infected with *Cyclospora*, the mean CD4 T cell count was insignificantly ($p < 0.05$) higher than that in patients with chronic diarrhea.

In accordance with our results, Navin *et al.* (1999) reported that CD4 cell counts play an incredibly important role in the presentation of diarrhea as well as in the control of protozoan infection in immunocompromised patients. They added that chronic diarrhea is typically associated with lower CD4 counts than acute diarrhea. Tuli *et al.* (2008) found that *Cryptosporidium* spp. was the most commonly acquired protozoa causing chronic diarrhea among HIV patients. They added that the CD4 cell counts were inversely proportional to the duration of diarrhea and patients with chronic diarrhea had lower CD4 counts than those who had acute diarrhea. Stark *et al.* (2009) stated that the outcome of infection by enteric protozoan parasites is dependent on absolute CD4 T cell counts, with lower counts being associated with more severe disease.

In conclusion, the present study clarified that enteric infections with opportunistic coccidian parasites (*Cryptosporidium*; *Cyclospora* and *Isospora belli*) are highly prevalent among diarrheic cancer patients in Saudi Arabia. Poly-parasitism is frequent. For all diarrheic immunocompromised and immunocompetent patients, special identification of these parasites must be ordered. The outcome of infection is dependent on absolute CD4 T cell counts, with lower counts being associated with more severe disease. So, optimizing the immunologic status of individuals who are at risk may help to reduce acquisition of such opportunistic parasitic infections and the likelihood of developing life-threatening diarrhea.

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