



Amoebiasis in Active Ulcerative Colitis: Epidemiological Aspects, Association and Impact of Anti-Amoebic Therapy on Disease Severity



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Abstract

Background and Aim: the incidence of ulcerative colitis (UC) is increasing worldwide. Several enteropathogens may be implicated in its pathogenesis. Amoebiasis is a common infection but it is overlooked or neglected especially in endemic regions. The study aimed to assess the frequency of *Entamoeba (E.) histolytica* in patients with active UC and evaluate the impact of the parasite and its therapy on disease severity.

Patients and Methods: Fresh fecal samples of 30 patients with active UC were examined for direct detection of *E. histolytica* cysts or trophozoites and its specific Ag (*E. histolytica* II) using ELISA. Colonoscopy and assessment of UC severity based on Mayo score and Montreal Classification were done. Patients with amoebiasis received anti-amoebic therapy and were followed up for 2 weeks.

Results: About 36.7% of those patients had amoebiasis. Amoebic infection was significantly higher in older age (P=0.048) and those with co-morbidities (P=0.001). Amoebiasis significantly associated with severe course (P=0.041, OR=1.2, 95%CI:0.2-2.1). Ten of eleven cases with amoebiasis had moderate/severe UC. On receiving anti-amoebic therapy, those patients showed clinical improvement with absent parasite in feces and mucosal healing in some cases.

Conclusion: Searching for amoebiasis in patients with active UC is important as it may be a trigger for UC exacerbation in endemic regions. Anti-amoebic therapy could be indicated for patients with persistent UC to avoid serious complications.

Keywords: Ulcerative colitis; Amoebiasis; *E. histolytica*; Exacerbation; Activity flare

Abbreviations: SD: Standard Deviation; CRP: C-Reactive Protein; UC: Ulcerative Colitis; ESR: Erythrocyte Sedimentation Rate; IGE: Infectious Gastroenteritis

Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory condition of the colonic mucosa characterized by a relapsing course that often requires long-term therapy to maintain remission [1]. A complex of genetic, immune and environmental factors may be implicated in UC pathogenesis. Additionally, the possibility of enteric pathogens in initiation or reactivation of the quiescent disease had been reported [2]. Management of UC is a significant clinical challenge as its active phase is associated with bloody diarrhea with mucus simulating infectious colitis also its treatment with immunomodulators and biological agents increases the risk of opportunistic infections and exacerbates

concomitant infections [3-5]. The frequency of these infections in UC patients is underestimated probably due to low index of suspicion or problems in their detection.

Amoebiasis is a common parasitic infection and globally about 50 million people are affected by *Entamoeba (E.) histolytica*, primarily in developing countries, with high annual fatality rate (over 100,000 deaths a year) [6,7]. It has been associated with autoimmune phenomena including antibodies to colonic epithelial cells and UC development [8]. Both amoebic colitis and UC constitute major health problems particularly in endemic areas for amoebiasis. Amoebic colitis can mimic acute phase of UC

causing misdiagnosis or coexist with UC causing missed diagnosis [3]. Missed or misdiagnosis of amoebic infection in UC patients receiving immunosuppressive agents may cause Fulminant colitis, bowel perforation and peritonitis with a high mortality rate [9]. Furthermore, Amoebiasis can exacerbate symptoms and adversely affect the course of UC [4]. So, screening for amoebiasis is crucial in patients with UC flares for accurate diagnosis and optimal treatment.

Earlier studies assessed the frequency and participation of several enteropathogens including amoebiasis in UC flares [3-5], however, these studies are deficient in our region. Egypt is endemic for amoebiasis with a high prevalence of 38% and it has an increasing incidence of UC in the last years so, distinguishing UC from amoebic colitis is important [6,7,10]. Therefore, we aimed to assess the epidemiological aspects of amoebiasis in patients with active UC, and the impact of the parasite and its therapy on the disease severity.

Patients and Methods

Study design

This cohort study was carried out prospectively at Assiut University Hospital, Assiut, Egypt between January 2019 and June 2019. The study was approved by the Local Ethics Committee of Assiut University Hospital (The ethical approval code was 17100958) and was conducted in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all the participants before enrollment.

Study population

During the study period, patients with well-defined active UC admitted to Gastroenterology and Tropical Medicine Department, Assiut University Hospital, Assiut, Egypt were consecutively included in the study. The diagnosis of UC and its activity was based on clinical, colonoscopic and histopathological findings [11,12], and the severity of UC activity was assessed by Mayo and Partial Mayo scores and Montreal classification [13,14]. Amoebiasis was diagnosed by the presence of the parasite and its specific antigen in stool. Patients known to have IBD other than UC or colorectal malignancies were excluded.

Methods

At study entry, thorough medical history and physical examination were taken for data collection e.g., age, sex, comorbidities, rectal bleeding, bloody diarrhea and its daily frequency and severity of disease. Laboratory investigations including complete blood picture, serum albumin, serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were done. Stool analysis for the presence of *E. histolytica* (trophozoites and/or cysts) and for detection of *E. Histolytica* Ag was one. In addition, colonoscopy and assessment of Mayo score were done for all participants.

Stool analysis

With universal safety precautions and standard laboratory protocols, fresh faecal samples were collected from each patient in a dry, clean, leak-proof plastic container to be examined for *E. histolytica*. Fresh and Formol-ether concentrated stool specimens were examined as saline and Lugol's iodine wet mount to detect motile trophozoites and cysts respectively. If Entamoeba parasite was identified in stool, ELISA detection of faecal *E. histolytica* adhesion antigen was used to confirm diagnosis using *E. histolytica* II assay "TechLab, Blacksburg, VA, USA" that was performed according to the manufacturer's instructions.

Follow up

Steroids were stopped for those patients with amoebic infection then they received a single oral dose of 500 mg of Secnidazole, anti-amoebic drug, and followed by oral diloxanide furoate (500 mg) three times daily for 10 days. Their response was evaluated within 2 weeks by clinical history and examination, assessment of Partial Mayo score and stool analysis for detection of the parasite and colonoscopy in some cases.

Statistical analysis

Statistical analyses were conducted using SPSS for windows version 16 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2010. The continuous data was expressed as means \pm standard deviation (SD) or median and range and was compared using Student's t test or Mann-Whitney U test. Categorical variables were expressed as a percentage and compared using chi-squared (χ^2) or Fisher's exact probability test. Multiple regression analysis was used to study the influence of independent variables on amoebic infection. Wilcoxon (two -related samples) test was used to compare the partial Mayo score in UC patients with positive *E. histolytica* Ag in response to anti-amoebic treatment. For all analyses, P value < 0.05 is statistically significant.

Results

Characteristics of the studied patients

A total of 30 patients with active UC were consecutively included in the study between January and June 2019. Their mean age was 34 ± 9.5 years and 53.3% were females. The extent of disease was extensive colitis (46.7%), left-sided colitis (36.7%) and proctitis (16.6%). Regarding severity of activity, 20 of the patients (66.7%) had moderate activity, 7 (23.3%) had mild activity, and 3 (10%) had severe disease. Apart from one patient who treated with infliximab, participated patients treated with conventional treatment (5-aminosalicylic acid with or without immunotherapy) for their disease. Detailed clinical and laboratory and endoscopic findings of the studied patients were summarized in Table 1.

Table 1: Clinical, laboratory and endoscopic findings of the studied patients.

	Total Patients with Active UC (n= 30)	Patients without <i>E. histolytica</i> Ag (n= 19)	Patients with <i>E. histolytica</i> Ag (n= 11)	P
Age (years)	34 ± 9.5 (19 - 52)	31.4 ± 9.2 (19 -52)	38.5 ± 8.8 (25 - 51)	0.048
Sex (M/F)	14/16 (46.7/53.3%)	9/10 (47.4/52.6%)	5/6 (45.5/54.5%)	0.919
Smoking	10 (33.3%)	6 (31.6%)	4 (36.4%)	0.789
Co-morbid diseases	13 (43.3%)	4 (21.1%)	9 (81.8%)	0.001
Duration of UC disease (years)	2.5 (0 - 5)	2 (0 - 5)	3 (0 - 5)	0.8
Diarrhea	28 (93.3%)	17 (89.5%)	11 (100%)	0.265
Rectal bleeding	23 (76.7%)	16 (84.2%)	7 (63.6%)	0.199
Frequency of diarrheal attacks/day	4 (3 - 7)	4 (3 - 6)	5 (3 - 7)	0.026
Frequency of previous disease attacks	28 (93.3%)	18 (94.7%)	10 (90.9%)	0.256
Serum albumin (g/dl)	3.2 (2.3 - 3.8)	3.2 (2.3 - 3.8)	3.3 (2.4 - 3.6)	0.759
Hemoglobin (gm/dl)	10.8 (7.8 - 15)	11 (7.8 - 15)	10 (8 - 14)	0.981
Leukocyte count (x10 ⁹ /l)	6.1 (2.4 - 17)	5.5 (2.4 - 17)	7 (4 - 12)	0.558
Platelet count (x10 ⁹ /l)	276 (117 - 579)	281 (117 - 579)	270 (156 - 412)	0.53
ESR (1st hour)	34 (7 - 85)	34 (7 - 85)	40 (18 - 85)	0.42
CRP	32 (8 - 108)	30 (8 - 108)	34 (22 - 62)	0.471
Disease extension				
Proctitis/Left-sided/Extensive colitis	5/11/14 (16.6/36.7/46.7%)	4/9/20/6 (21.1/47.4/31.7%)	1/2/10 (9.1/18.2/72.7%)	0.187
Prominent colonoscopic lesion				
Mucosal hyperaemia	5 (16.7%)	2 (21.1%)	1 (9.1%)	
Mucosal ulceration(s)	19 (63.3%)	12 (63.2%)	7 (63.6%)	0.787
Pseudopolyps	2 (6.7%)	1 (5.3%)	1 (9.1%)	
Mixed lesions	4 (13.3%)	2 (10.5%)	2 (10.5%)	
Mayo score	9 (4-12)	9 (4 - 10)	11 (4 - 12)	0.043
Partial Mayo score	6 (3 - 9)	6 (3 - 7)	7 (3 - 9)	0.023
Severity of UC*				
(Mild/Moderate/Severe)	7/20/3 (23.3/66.7/10.0%)	6/13/20/0 (31.6/68.4/0%)	1/7/3 (9.1/63.6/27.3%)	0.035
Duration of UC treatment (years)	2 (0 - 4)	2 (0 - 4)	2 (0 - 4)	0.767
Treatment lines for UC				
5-ASA	7 (23.3%)	6 (31.6%)	1 (9.1%)	
5-ASA and steroid	19 (63.3)	11 (57.9%)	8 (72.7 %)	0.322
5-ASA, steroid and azathioprine	3 (10%)	2 (10.5%)	1 (9.1%)	
Infliximab	1 (3.3%)	0	1 (9.1%)	

Values were presented as mean ± standard deviation, median and range or n (%). P value < 0.05 means significant. CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; UC: Ulcerative Colitis

Diagnosis of amoebic infection

On fecal examination, amoebic infection was identified in 36.7% of patients (6 females and 5 males with mean age of 38.5 ± 8.8 years), where, trophozoites were detected in two cases, cysts

in seven cases and both trophozoites and cysts in further two cases. Furthermore, the presence of *E. histolytica* was confirmed with fecal detection of its specific Ag in these cases. Details of characteristics of ulcerative colitis patients with *E. histolytica* Ag were shown in Table 2.

Table 2: Details of characteristics of ulcerative colitis patients with *E. histolytica* Ag.

No	Age	Sex	Smoking	Disease Duration (years)	Co-morbid diseases	Blood in stool	Mayo score	Partial Mayo score	Treatment	<i>E. histolytica</i> in stool	Colonoscopic Features		Response to Anti-Amoebic TTT *	Post Anti-Amoebic Treatment Partial Mayo score
											Extension site	Prominent lesion		
1	48	M2	Yes	5	CLD	Yes	12	9	5-ASA Steroid	Cyst	Pancolitis	Mixed	Yes	6
2	28	M	Yes	3	CLD	Yes	11	8	5-ASA Steroid	both	Extensive colitis	Ulceration	Yes	5
3	39	F	No	3	DM	Yes	11	8	5-ASA Steroid	both	Extensive colitis	Pseudo-polyps	Yes	5
4	36	M	Yes	2	No	Yes	10	7	5-ASA Steroid	Cyst	Extensive colitis	Ulceration	Yes	4
5	37	M	Yes	2	Cardiac	No	4	3	5-ASA	Trophozite	Proctitis	Hyperaemia	Yes	2
6	28	F	No	3	No	No	11	8	5-ASA Steroid	Trophozite	Lt sided colitis	Ulceration	Yes	5
7	41	F	No	5	DM	No	12	9	5-ASA Steroid Aza-thio-prine	Cyst	Extensive colitis	Ulceration	Yes	6
8	51	F	No	1	DM, cardiac	Yes	8	5	5ASA Steroid	Cyst	Lt sided colitis	Mixed	Yes	3
9	48	F	No	3	Renal	No	9	6	5-ASA Steroid	Cyst	Extensive colitis	Ulceration	Yes	3
10	25	M	No	0	CLD	No	12	9	Infliximab	Cyst	Extensive colitis	Ulceration	Yes	7
11	42	F	No	2	Cardiac	No	8	5	5-ASA Steroid	Cyst	Extensive colitis	Ulceration	Yes	3

*Anti-amoebic treatment by secnidazole 500mg (4 tablets a single oral dose) and response to treatment in the form of clinical improvement and absence of parasite in stool

CLD: Chronic Liver Disease; DM: Diabetes Mellitus; HTN: Hypertension; 5-ASA: 5-Aminosalicylic acid

Comparison between patients with and without amoebic infections

Compared to those without amoebiasis, patients with amoebiasis were significantly older age where 45.5% of these cases were older than 40 years. In addition, co-morbidities, frequency of diarrheal attacks per day, severity of the disease based on Montreal classification, Mayo and partial Mayo scores were significantly higher in patients with amoebic infection compared to those without infection. However, gender and other clinical and laboratory parameters had no significant differences

between two groups (Table 1).

Association between severity of ulcerative colitis and amoebic infection

The presence of amoebiasis was significantly associated with moderate/severe UC (0.041). Ten out of eleven cases (90.9%) with *E. histolytica* had moderate/severe UC, while 13 out of 19 cases (68.4 %) without *E. histolytica* had moderate/severe UC (Table 3). Detection of *E. histolytica* in stool was associated with a relative risk for moderate/severe UC of 1.2 (95% CI: 0.2 to 2.1) compared to patients without detectable *E. histolytica*.

Table 3: Association between severity of ulcerative colitis and amoebic infection.

<i>E. histolytica</i>	Active Ulcerative colitis		P
	Severe/moderate (n= 23)	Mild (n=7)	
Yes (n= 11)	10 (90.9%)	1 (9.1%)	0.041
No (n= 19)	13 (68.4%)	6 (76.7%)	

Follow-up ulcerative colitis patients with amoebic infection

On receiving the anti-amoebic therapy, those patients clinically improved e.g, decrease the frequency of daily diarrheal attacks, decrease blood amount in stool, improved their general condition

and absence of fecal parasite with colonoscopic mucosal healing in some cases (Figure 1). In addition, those patients receiving anti-amoebic treatment showed significant improvement in their partial Mayo scores [pre-treatment score 7 (3 - 9) vs. post-treatment 5 (2 -7), P < 0.001] as shown in Figure 2.



Figure 1: Colonoscopic findings of a patient with ulcerative colitis and positive stool *E. histolytica* Ag a) before anti-amoebic therapy (hyperemic mucosa with ulcerations) b) after anti-amoebic therapy (mucosal healing disappearance of ulcerations).

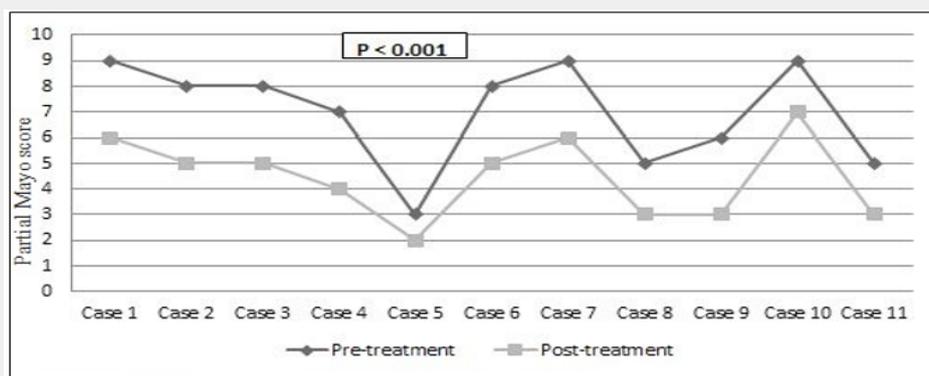


Figure 2: Response to anti-amoebic therapy in ulcerative colitis patients with amoebiasis.

Discussion

This study aimed to highlight the epidemiological aspects of amoebiasis in patients with active UC, and the impact of the parasite and its therapy on disease severity. Egypt has a high prevalence of amoebic infection [4,7], and a limited published

data on amoebiasis and its relation to UC activity coexist so, it was encouraged to be carried out on that special population. Infection may contribute in the ethiopathogenesis of UC affecting the colonic mucosa with disarrangement in its immunity [9]. Amoebic infection is usually overlooked or underestimated due

to diverse clinical and colonoscopic presentations of amoebic colitis confusing with other types of colitis including UC in addition to difficulty in its definitive diagnosis with absence of fecal trophozoites and cysts in some cases [4,15]. Detection of *E. histolytica* by identifying both the parasite and its specific Ag in stool, as in our cases, supports the diagnostic utility and enhances the sensitivity to definite detection of amoebic infection [15]. Our analysis identified amoebiasis in 36.7% of thirty patients with active UC. Our result was higher than that mentioned in previous studies in Mexico (5%), Turkey (17.2%), and Bosnia and Herzegovina (14.3%) owing to its endemicity in our area along with various environmental and socioeconomic factors [5].

This study corroborates that age, co-morbidities and disease severity were independently associated with amoebiasis in those patients that were in agreement with previous studies [16-18]. We found that UC patients with amoebiasis were significantly older than those without, where 45.5% of cases were over 40 years old because of their poor health and higher frequency of co-morbidities that increased their susceptibility to infection. These findings were consistent with earlier reports that showed that the peak rate of amoebiasis occurred between 40 and 49 years [17]. In line with previous studies [4,19], in those UC patients, amoebiasis were significantly associated with severe course that can be explained by mucosal disruption facilitating mucosal invasion of trophozoites and worsening the clinical and endoscopic conditions [16]. Babic et al., [4] documented that hyperactivity of the mucosal immune system to the intraluminal antigens e.g., *E. histolytica* can initiate or reactivate quiescent disease in IBD. Schulzke et al., [20] reported that infectious gastroenteritis (IGE) may exacerbate IBD increasing its risk (OR= 1.40, 95% CI: 1.19 - 1.66). In addition, the increased use of immunomodulators and biological agents can increase the risk of enteropathogens including amoebiasis among those patients [4]. These data indicate that stools from UC patients should be examined before planning optimal medical therapy. Contrary to our finding, Vukobrat-Bijedic et al., [18] found that disease severity was not associated with amoebic infection in UC patients.

Consistent with the earlier series [21-23], in this study, treatment of infected patients with anti-amoebic therapy showed symptomatic improvement and colonic mucosal healing in some cases. Collins and Bynum [21], treated four UC patients with amoebiasis by medications for both diseases and observed a good response. However, Brown & Winkelman [22], treated two UC patients with amoebiasis with anti-amoebic therapy resulting in clinical and endoscopic improvement with abolition of colectomy decision in one of those two patients. Underwood [24] and Shirley & Moonah [25] concluded that this concomitant amoebiasis should always be considered before administering corticosteroids and/or immunosuppressive therapy especially in UC patients residing in endemic areas or with a travel history. Therefore, an empirical trial of anti-amoebic therapy should be recommended in persistent or relapsing IBD, especially in endemic areas that may reduce or prevent serious complications

or unneeded critical management as colectomy. In this study, secnidazole was administered in a single oral dose that was better tolerated with a high cure rate making it a suitable option to other single-dose treatments and an attractive alternative to multiple dose regimens with other drugs in this class [15,26]. This study has certain strengths and limitations. This is one of the very few studies that have searched for amoebic infection as a trigger for UC exacerbations and the effect of its treatment on disease severity in this endemic area where the majority of previous studies discussed amoebiasis in patients who lived in developed countries and had a travel history. In addition, amoebic infection was diagnosed by detecting the parasite and its specific Ag in stool to differentiate it from non-pathogenic organisms e.g., *E. dispar* or *E. moshkovskii*s and to distinguish new from past infection in our region where seroprevalence is high. Single dose of anti-amoebic drug "secnidazole" was highly effective and tolerated in those patients who were exhausted by frequent medications. On the other hand, there were some limitations to this work. It was a small sample sized and single-centre study however, it carried out in Assiut University Hospital; a tertiary care centre, where cases of persistent or relapsing UC is more possible to be admitted. Colonoscopic mucosal biopsies for detection of the parasite were not taken for fear of perforation during air insufflations to expand the colon in those patients with UC flares. So, large multicenter cohort studies will be emphasized to confirm these findings.

Conclusion

Intestinal amoebiasis was presented in 36.7% of patients with active UC that may contribute to in its activity flare or persistence despite optimal medical treatment of UC. Searching for *E. histolytica* is recommended in every patient with UC to rule out missed or misdiagnosis. A trial of anti-amoebic therapy may be indicated for any patient with persistent UC to avoid serious complications.

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