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Colonic involvement in amebic liver abscess: does site matter?

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Abstract

Background Colonic involvement in amebic liver abscess (ALA) occurs in more than half of the patients. However no studies have found any association between the site of the colonic lesions and location of abscesses in the liver. Thus, the present study was designed to find the correlation between colonic involvement in solitary and multiple ALAs.

Methods This is a case control study of 80 patients allocated in two groups, the first with solitary (controls) and the second with multiple ALAs (cases). Colonoscopy was performed in all patients enrolled in the study.

Results Solitary ALA was seen in 70% of patients whereas multiple ALAs in 30%. Colonic involvement in the form of erythema, inflammation and ulceration was seen in 77.5% of cases of ALA. 71.4 % cases of solitary ALA had colonic lesions compared to 91.6% cases of multiple ALAs (P=0.02). Most of the patients with multiple ALAs had involvement of the transverse and right colon (75%). Involvement of right colon was present in all patients with colonic involvement. A significant involvement of the right and transverse colon was seen in cases of multiple compared to solitary ALA (P<0.0001).

Conclusion Colonic involvement is present in more than two thirds of patients with ALA. When colonic involvement is present, right colon lesion is universally present. Colonic involvement may extend beyond hepatic flexure in patients with multiple amebic ALAs, either involving right hepatic lobe or both lobes.

Keywords Amebic liver abscess, superior mesenteric vein, inferior mesenteric vein

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Introduction

Amebiasis is an infection with intestinal protozoa *Entamoeba histolytica* [1,2]. More than 85% of infections are asymptomatic and the remaining 10% produce a clinical spectrum ranging from dysentery to abscesses of liver (ALA) or other organs. Amebiasis constitutes an important global problem in the tropics and subtropics, affecting approximately 12% of the world's population at any time [3]. Various risk factors such as poor hygiene, diabetes mellitus, steroid overuse, chronic alcoholism and human immunodeficiency virus infection have been known to predispose to the development of ALA [4-7]. Most patients present with an acute illness and duration of symptoms lasting less than 2 weeks. The main presenting features are abdominal pain, fever, and anorexia. It primarily affects the colon but the liver is the most common extraintestinal organ involved [8,9]. The parasite has been shown to be carried to the liver from the large bowel via the portal venous system [10]. Hence one would expect the colon to be effected in all cases of ALA, but diarrhea is observed only in one third [11]. It is possible that most patients with ALA have asymptomatic involvement of the colon. In an autopsy series by Aikat *et al* [12], ulceration of the large bowel was seen in 59% of cases of liver abscess. Sachdev and Dhol reported colonic involvement in 58% of cases with ALA [13]. In a more recent study by Mishra *et al* colonic ulcerations were seen in 55% of cases of ALA and it was more likely to occur in the presence of active diarrhea or in the recent past [14]. The site of liver abscess is determined by the point of entry of the parasite in the colon, because of streamlining of blood flow in the portal venous system [15,16]. However, recent studies have not found any association between the site of the colonic lesions and location of abscesses in the liver [13,14]. Therefore, a study was conducted to find the correlation between colonic involvement in solitary and multiple ALAs.

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Conflict of Interest: None

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Patients and methods

A case control study was conducted at the Department of Gastroenterology, SNMC Jodhpur over a period of 12 months from June 2012 to May 2013. Ninety two patients were enrolled in the study; 12 patients were excluded. Two patients did not give consent for colonoscopy while full length colonoscopy could not be done on 4 patients. One patient developed spontaneous right pleural communication following rupture and was managed by percutaneous intercostal drainage tube placement. Five patients had impending rupture and had to be treated with percutaneous drainage tube placement. Finally, 80 patients were included, comprising 56 patients with solitary (70%) and 24 patients with multiple ALAs (30%). The study was approved by the ethics committee of the medical college. After written consent was obtained in accordance with the Helsinki declaration, patients were counselled and explained about the objectives of the study by a qualified medical doctor. Detailed personal history was taken using a standard questionnaire and a 5 mL blood sample was collected. Inclusion criteria comprised presence of clinical features suggestive of ALA (fever, right upper abdominal pain, tender hepatomegaly); ultrasonography finding of single or multiple hypoechoic lesion(s) in the liver and elevated anti-amebic antibody titer (IgG>160, immunofluorescent assay). Diagnosis was established by the presence of all the three clinical, imaging and serological parameters. Exclusion criteria included sick patients who were unfit for colonoscopy, patients receiving anti-amebic treatment in the preceding 8 weeks and patients who denied consent. A detailed clinical history of diarrhea in the recent past (8 weeks) and presence of risk factors (alcohol intake, diabetes mellitus, and human immunodeficiency virus status) were recorded.

Colonoscopy was performed in all patients at admission or within 48 h of starting anti-amebic treatment. In all 80 patients, colonic preparation was performed by ingestion of a polyethylene glycol electrolyte solution. Colonoscopy was performed with the patient under conscious sedation (Diazepam 5-10 mg or Midazolam 2-3 mg) administered intravenously. During colonoscopy a detailed mucosal lesion of erythema and ulcers were noted, and if ulceration was present then details of size, location and surrounding inflammation of the ulcers were recorded. Ulcer size less than 3 cm was considered discrete or small whereas size more than 3 cm was considered large. Ulcer size was determined using an endoscopic measuring wire designed for endoscopic retrograde cholangiopancreatogram to assess length (Wilson-Cook). Multiple biopsy specimens were obtained from the ulcer margins and histopathological examination was done.

Statistical analysis

Parametric data are expressed as mean values ± standard deviation (SD) and categorical variables as percentages. The chi-square test or Fisher's exact was used for the comparison of dichotomous variables and the Student's *t* test for continuous variables. A P value <0.05 was considered statistically significant. All data were analyzed using the SAS 8.0 statistical package.

Results

Patient characteristics

Eighty patients were divided into two groups, one with solitary (70%) and the other with multiple ALAs (30%). Mean age was 36.6 years with a strong male predisposition (M:F=9:1). Risk factors were present in 35% cases of ALA and included alcohol intake >40 g/day (22.5%) and presence of diabetes mellitus (12.5%). Risk factors were commonly associated with multiple ALAs (Table 1). However no case of HIV with ALA was seen during the study period. Most of the patients had symptom duration of 2-4 weeks and no patient was seen with symptoms beyond 6 weeks. Most of the patients with multiple ALAs were symptomatic within 2 weeks. Pain in right hypochondrium was the most common symptom (97%), followed by fever (95%) and nausea/vomiting (25%). Diarrhea was present in less than one fourth of the patients (22.5%). Jaundice was seen in only 5% and was more common in patients with multiple ALAs, although statistically non-significant. Most of the patients had a high total leukocyte count and mildly raised alkaline phosphatase, but were comparable in both the groups. ELISA test with an anti amebic titer >1:160 was taken as positive for *Entamoeba histolytica*. The titer had been validated in other studies conducted in India [14], however a titer greater than 1:400 is considered strong for ALA. Stool for cyst and trophozoites were positive in only 4 (5%) patients. It was seen only among the patients with active or recent diarrhea.

ALA

Solitary ALA was seen in 56 (70%) subjects whereas multiple ALAs in 24 (30%) subjects. Most of the lesions were localized in the right lobe of liver (85%), the left lobe was involved in 10% and there was bilobar involvement in 5% cases (Table 2). Twenty cases (83.3%) of multiple ALAs had only involvement of the right lobe of liver, whereas in the remaining 4 cases (16.7%) there was bilobar involvement. In solitary ALA, the right lobe of liver was involved in 85.7% and left lobe involvement was seen in 16.3%. There was no case of multiple ALAs involving only the left lobe of liver.

Colonic lesions

Colonic involvement in the form of erythema and ulceration was seen in 62 (77.5%) patients of ALA whereas no abnormality was seen in 18 (22.5%) patients. Cecum (70.9%) was the most common site of colonic involvement followed

Table 1 Baseline characteristics

Parameters	n=80 (%) Mean ± SD	Solitary (%) n=56 (70) Control	Multiple (%) n=24 (30) Cases	P value*
Age (Mean ± SD)	36.6 ± 7.8	35.8 ± 8.1	37.5 ± 7.6	0.19
Male: Female	9:1	50:6	22:2	0.10
Risk factors				
Alcohol	18 (22.5)	8 (14.2)	10 (41.6)	0.02[a]
DM	10 (12.5)	4 (7.1)	6 (25)	0.03[a]
HIV	0 (0)	0 (0)	0 (0)	
Symptom duration (weeks)				
0-2	28 (35)	12 (21.4)	16 (66.6)	0.004[b]
2-4	46 (57.5)	40 (71.4)	6 (25)	0.3
4-6	6 (7.5)	4 (7.1)	2 (8.3)	0.11
Symptoms/Signs				
Fever	76 (95)	53 (94.6)	23 (95.8)	0.11
Abdominal pain	78 (97)	55 (98.2)	23 (95.8)	0.13
Diarrhea	18 (22.5)	12 (21.4)	6 (25)	0.10
Anorexia/Nausea	20 (25)	13 (23.2)	7 (33.3)	0.09
Jaundice	4 (5)	1 (1.8)	3 (12.5)	0.06
Pallor	6 (7.5)	3 (5.3)	3 (12.5)	0.07
Rales	20 (25)	12 (21.4)	8 (33.3)	0.06
Hemoglobin (g/dL)	11.2 ± 1	11.2 ± 1.2	11.2 ± 0.8	0.47
Total leukocyte count (cells/cm^3)	13229 ± 2023	12832 ± 2218	13627 ± 1828	0.06
Platelets (10^5/dL)	3.37 ± 0.48	3.34 ± 0.54	3.40 ± 0.43	0.34
Serum bilirubin (mg/dL)	1.18 ± 0.40	1.12 ± 0.31	1.25 ± 0.50	0.08
Aspartate aminotransferase (u/L)	41.4 ± 15.2	42.6 ± 15.9	40.1 ± 14.4	0.25
Alanine aminotransferase (u/L)	33.2 ± 6.5	34.5 ± 8.9	31.8 ± 4.1	0.07
Alkaline phosphatase (u/L)	409.5 ± 109.9	393.5 ± 102.6	425.4 ± 117.1	0.11

**P values were determined using the Fisher's exact test for categorical variables and Student's t test for continuous variables. [a]P value < 0.05, [b]P value <0.01; DM diabetes mellitus; HIV human immune deficiency virus*

by lesions involving both right colon with transverse colon (35.4%) and isolated ascending colon (22.5%). There were no cases of isolated transverse colon involvement, but involvement of right colon was present in all patients with colonic involvement. Colonic lesions were more commonly seen with multiple than solitary ALA (Table 3). In patients with solitary ALA, cecum involvement (46.4%) was seen most commonly followed by isolated in the ascending colon (17.9%) and right plus transverse colon (7.1%). Most of the patients with multiple ALAs had involvement of the transverse and right colon (75%), while isolated right colon was involved in 16.6% patients. Among the 18 patients of multiple ALAs with lesions involving transverse colon, 16 had cecal lesions and two had lesions in the ascending colon. A significant involvement of the right and transverse colon was seen in cases of multiple ALAs compared to solitary ALA (P<0.0001). Histological analysis of the colonic biopsy was done in all subjects with colonic lesion; flask-shaped ulceration and acute inflammatory cells were seen commonly but trophozoite invading the lamina propria was seen in only 10 (16.1%) patients.

Table 2 Lobes of liver involved in amebic liver abscesses (ALAs)

Liver involvement	n=80	Solitary ALA n=56 (70%)	Multiple ALAs n=24 (30)	P value
Right lobe	68 (85)	48 (85.7)	20 (83.3)	0.07
Left lobe†	8 (10)	8 (14.3)	0 (0)	
Right *plus* left lobe	4 (5)	0 (0)	4 (16.7)	

† No case of multiple ALAs involving only left lobe of liver

Table 3 Colonic involvement in amebic liver abscesses (ALAs)

Colon segment	n=80	Solitary ALA n=56 (%)	Multiple ALAs n= 24 (%)	P Value
Colon lesion (involved)	62 (77.5)	40 (71.4)	22 (91.6)	0.02[a]
Isolated cecum	44 (70.9)	26 (46.4)	2 (8.3)	0.0004[b]
Isolated ascending colon	14 (22.5)	10 (17.9)	2 (8.3)	0.15
Isolated transverse colon†	0 (0)	0 (0)	0 (0)	
Transverse colon + right colon	22 (35.4)	4 (7.1)	18 (75)	<0.0001[b]
Colonic lesions (cm)	62 (100)	40 (100)	22 (100)	
<3 (small)	48 (77.4)	26 (65)	22 (100)	0.0004[b]
>3 (large)	36 (58.1)	21 (52.5)	15 (68.1)	0.12

[a]P value <0.05, [b]P value <0.01; † No cases of isolated transverse colon involvement

Small colonic ulcers (<3 cm) were seen in 77.4% of cases of ALA compared to large ulceration (>3 cm) in 58.1% of patients. Small ulcerations were seen in the cecum, ascending colon or hepatic flexure without any surrounding hyperemia (Fig. 1A). Small ulcerations were universal among cases of multiple ALAs whereas it was seen in 65% cases of solitary ALA (P=0.0004). Large ulcers were commonly associated with surrounding hyperemia and small ulcerations (Fig. 1B). Large colonic ulceration was also more common in patients with multiple (68.1%) compared to solitary ALA (52.5%), although statistically non-significant (P=0.12).

Discussion

The incidence of ALA has been reported to vary between 3% and 9% of all cases of amebiasis [17]. In India ALA is endemic and occurs most commonly in the age group of 20-45 years. It has been noted infrequently at the extremes of age and is seven to nine times more common in males [18]. In our study the mean age group for ALA was 36.6 years and with a strong male predisposition (M:F=9:1). There was a significant risk of developing both solitary and multiple ALAs in patient consuming alcohol >40 g/day or with the presence of diabetes mellitus. Either of the risk factors was present in one third of the patients with ALA (35%) but there was no case of HIV infection or long-term immunosuppressive mediation. Katzenstein *et al* reported in their study that 25% of male patients with ALA were chronic alcoholics [19]. However, the pathogenesis of ALA in chronic alcohol intake is still unclear. Makkar *et al* stated that a higher incidence of ALA in alcoholics was possibly due to higher hepatic iron content [20]. In our present study both chronic alcohol intake and diabetics were commonly seen; so we presumed that fatty liver commonly seen in both the clinicopathological conditions may make the hepatocytes vulnerable for trophozoite invasion and resistance. Pathogenic isolates in the favorable environment may be an additional factor in the development of liver abscess. Further work is warranted for establishing the pathogenesis of ALA in alcoholics or diabetics.

ALA may present as an acute process or as a chronic indolent disease. Most patients present with acute illness and duration of symptoms of less than 2 weeks. In the pres-

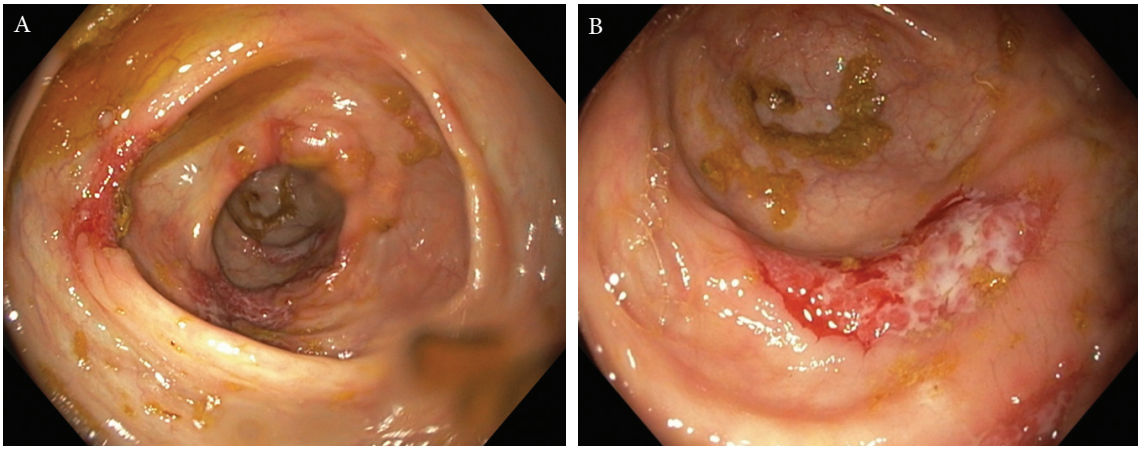

Figure 1 (A, B) Colonoscopy view of large and small ulcerations

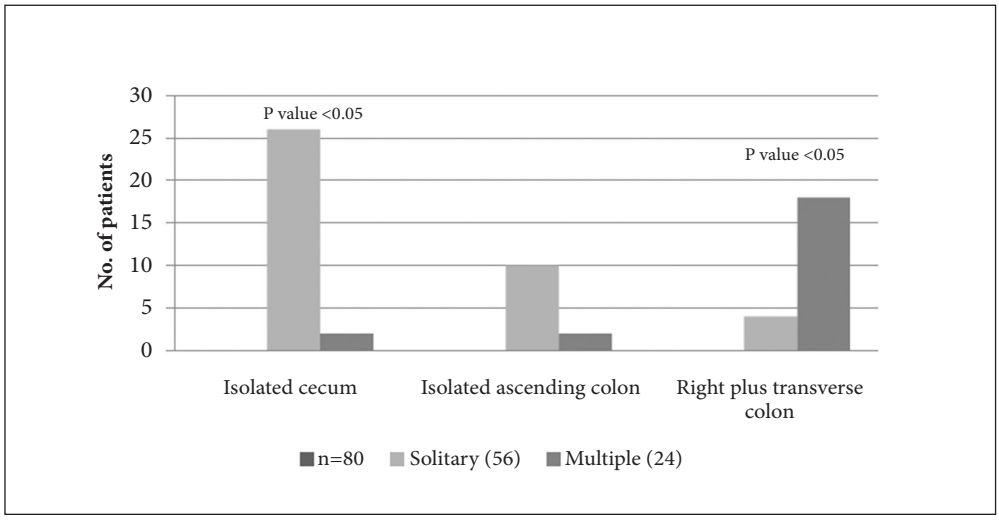

Figure 2 Colonic involvement in amebic liver abscesses

ent study, most of the patients with solitary ALA presented with symptoms for 2-4 weeks compared to less than 2 weeks duration in patients with multiple ALAs. The main presenting features were abdominal pain (97%), fever (95%), and anorexia/nausea (25%). Abdominal pain is usually moderate and localized to the right upper quadrant or to the epigastrium. Diarrhea was present in less than one fourth of the patients (22.5%), comparable to previous studies [2,3]. Stool for trophozoites or cysts was seen in only 5% patients, suggesting that most of the active colonic infection disappears by the time patients present with ALA. Jaundice was more commonly seen in cases of multiple ALAs compared to cases of solitary ALA. Overall jaundice was seen in 5% of cases with ALA. Previous studies have shown that during the course of illness one-third of patients may develop clinical jaundice. Severe jaundice is usually due to a large abscess or multiple abscesses, or to an abscess situated at the porta hepatis [21]. In the present study, 70% of cases pertained to solitary and the rest 30% multiple ALAs with right lobe of liver involvement in 85%, left lobe in 10% and bilobar involvement in 5% cases. Right lobe of liver was commonly involved in both solitary and multiple ALAs. This is similar to those observed in other studies in India showing that ALAs usually occur in the right lobe of the liver and are solitary (30-70%), while 15% of patients may have multiple ALAs [18].

Colonic ulcerations (small and large ulcers) were seen in 62 (77.5%) patients with ALA, these lesions were significantly more common in patients with multiple ALAs (91.6% vs. 71.4%, P=0.03). Sachdev and Dhol reported colonic involvement in 58% of cases with ALA while Mishra *et al* reported colonic ulcerations in 55% of cases of ALA and it was more likely to occur in the presence of active diarrhea [13,14]. The colonic ulcerations were more commonly small (<3 cm) and they were commonly present in patients with multiple as compared to solitary ALA (P=0.0004).

Liver hemodynamics is characterized by a dual venous and portal blood supply whose physiologic variations are particularly evident during digestion. In the normal subject portal blood flow is laminar with the right liver receiving the blood from the small intestine while the left liver is supplied by the blood from the spleen and colon [15,16]. Because the colon is the primary site of infection by parasites, it is likely that colonic lesions may be the portal of entry. The parasite may traverse through the colonic lesion to the superior mesenteric vein (SMV) or inferior mesenteric vein (IMV) and then finally through the right or left portal vein into the liver parenchyma. In the present study right colon was universally involved in patients with ALA with colonic involvement. Cecum involvement (70.9%) was seen commonly followed by right colon plus transverse colon (35.4%) and isolated ascending colon (22.5%). There was a significant involvement of the transverse colon along with right colon in the patients comprising multiple ALAs as compared to patients with solitary ALA (P=0.0002). This study for the first time shows a correlation of patchy involvement of colonic mucosa beyond the hepatic flexure might act as a portal of entry to SMV and IMV, and may finally lead to multiple ALAs either in right lobe or in both lobes of liver. This justifies the previous hypothesis of liver hemodynamics that portal blood flow is streamlined or laminar with the right liver receiving blood from the small intestine and the left liver receiving blood from the spleen and colon.

In conclusion the present study demonstrates that colonic involvement is present in more than two thirds of patients with ALA. When colonic involvement is present, a right colon lesion is universally present. Colonic involvement may extend beyond the hepatic flexure in patients with multiple ALAs, either involving the right or both lobes of the liver.

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Summary Box

What is already known:

- Colonic involvement in amebic liver abscess occurs commonly
- Colonic lesions in amebic liver abscess involve cecum and ascending colon
- Portal of entry of the parasite by superior or inferior mesenteric vein

What the new findings are:

- Colonic involvement in amebic liver abscess occurs in more than three quarters of cases
- Amebic liver abscess with colonic lesion have universal involvement of cecum or ascending colon
- Colonic involvement may extend beyond hepatic flexure in multiple amebic liver abscesses

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