Clinical and Endoscopic Management of Synchronous Amoebic Liver Abscess and Bleeding Colonic Ulcers

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Abstract
Background. Intestinal amebiasis is endemic in India, with myriad clinical presentations. The liver is the most common extra-intestinal organ to be involved in invasive amoebiasis up to 37% of cases. Synchronous presentation of hepatic and intestinal disease is unusual, and presentation as acute gastrointestinal bleed, or amoeboma even more atypical.

Goals: We aimed to assess the frequency of synchronous hepatic and colonic amebiasis and the efficacy of endoscopic management of colonic bleeding.

Results: We screened 52 consecutive patients with amebic liver abscess for synchronous intestinal amoebiasis and report the clinical course of 28 patients (mean age 48.3 years, all male) with amoebic liver abscess (ALA), (mean size, 7.2 ± 2.8 cm) who presented to us with lower gastrointestinal bleed requiring endotherapy. Patients with synchronous infection had higher bilirubin, liver enzymes and prothrombin time. Most needed percutaneous drainage of the liver abscess, and had prolonged hospital stay. They had ileocaecal ulcers with active bleeding; ulcer with adherent clot in 10(50%), and visible vessel in 8(37.5%), or active ooze in 4(12.5%). One patient had an ulcerated rectal mass, which appeared malignant on endoscopy, which was later found to be an amoeboma on microscopy. Hemostasis was achieved with dilute epinephrine injection, one patient required argon plasma coagulation, and 4 subjects required haemoclip placement at the site to control ooze from a visible vessel.

Conclusion: Synchronous hepatic and intestinal amebiasis is not uncommon, and often requires endoscopic haemostasis in case of gastrointestinal bleeding due to colonic disease. We report the successful endoscopic control of bleeding amoebic ulcers in all 24 patients.

Introduction
Intestinal amebiasis is endemic in India, but has been reported worldwide.1 The liver is the most common extra-intestinal organ to be involved in invasive amoebiasis in up to 37% of cases.2,3 Conversely, two studies from India reported that colonic ulcers have been associated with the liver abscess, even in asymptomatic subjects in 55% of patients with ALA.4,5 These ulcers are more common in patients with both acute or those with resolving or quiescent diarrhoea.6 Formation of an amoeboma has been reported in only about 1.5% of all cases.6 Although there have been recent reports dealing with the problem of bleeding in amoebic ulcers, the synchronous presentation of complicated liver abscesses and colonic bleeding is rare. An amoeboma is a rare complication of amoebic colitis, which presents as a mass or growth on colonoscopy.7 On histology, is seen as a mass of granulation tissue in the bowel wall with peripheral fibrosis with a mixed inflammatory infiltrate secondary to chronic amoebic infection.8 The initial presentations are usually obstruction and gastrointestinal bleeding. The most common sites are the ascending colon and the caecum, followed by the sigmoido-rectum.9,10 In view of better availability of diagnostic facilities like ultrasonography, an increasing number of patients are being diagnosed early and found to have synchronous intestinal and liver amoebiasis.11

Patients and Methods
We screened consecutive patients with liver abscess who presented at the out-patient hepatology clinic at the Institute of Liver and Biliary Sciences (ILBS) between July 2016 and January 2017, for evidence of synchronous intestinal amebiasis. All patients were enrolled with written informed consent for this observational study in accordance with the Declaration of Helsinki, and approval was taken from the Institutional Ethics Committee. The diagnosis of amoebic liver abscess was determined on the basis of the clinical presentation with fever, right upper abdominal pain, tender hepatomegaly, with typical imaging findings of a single or multiple hypoechoic lesion(s) in the liver and antiamebic IgG titre >1: 160 in serum using immunofluorescent assay. They underwent ultrasound examination of the liver and basic blood investigations including tests like complete blood count, coagulation profile, liver function tests, and serologies for amoebiasis and echinococcosis, iron profile, serum ferritin, and other relevant tests. All patients underwent a colonoscopic examination with targeted biopsies for histopathological examination. In patients with large liver abscesses with impending rupture, interventional radiology opinion was taken regarding the need for drainage and percutaneous drains would be

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placed where necessary. Evaluation for the other common causes of clinical bleeding included history of over the counter medication use, over-diuresis, alcohol intake, use of complementary and alternative medications, and serology for hepatotropic virus infections.

Statistical analysis
We used SPSS v.12 by IBM for Windows to perform all of the statistical calculations. For each variable, we calculated the normality, means and standard deviations. The Student’s t-test was used to compare the two groups, with normal distribution. The Wilcoxon-rank sum test was applied for data with a non normal distribution. Results were considered significant if the P value<0.05.

Results
We report a series of 52 consecutive patients with amoebic liver abscess (ALA), of which 28 male patients had concomitant intestinal disease, and 24 had ALA alone. Thus synchronous disease was noted in up to 53.8% of all patients. Twenty (71.4%) of patients with synchronous amoebiasis had large ileocecal ulcers, which resulted in intermittent fresh bleeding per rectum in 16 (80.0%), requiring transfusion and also endoscopic intervention. One patient had an ulcerated rectal mass, which appeared malignant on endoscopy, which was later found to be an amoeboma on histopathological examination. In addition, six patients had sigmoidal rectal ulcers, which also presented with fresh bleeding per rectum. The mean age of these patients was 48.3 ± 4.2 years (range 24 to 48 years). These 20 patients presented with active bleeding as the primary symptom and were incidentally found to have liver abscesses. Conversely, 8 patients presented with a liver abscess and severe anemia, and on questioning admitted to fresh bleeding per rectum. As demonstrated in Table 1, these patients had higher AST, ALT and bilirubin as compared with liver abscess alone. They also had a tendency to develop acute kidney injury due to volume depletion, increased transfusion requirements and electrolyte imbalances. All of them were found to have ileocaecal ulcers with active bleeding; ulcer with adherent clot in 10(50%), and visible vessel in 8(37.5%), or active ooze in 4 (12.5%).

Table 1: Comparison between synchronous hepatic and intestinal amoebiasis patients and the control group with amebic liver abscess alone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case: Synchronous Liver + Colonic Disease (N=28)</th>
<th>Control: Liver abscess alone (N= 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.3 ± 4.2</td>
<td>46.5 ± 13.7</td>
<td>0.498</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>95.8%</td>
<td>0.554</td>
</tr>
<tr>
<td>Haemoglobin g/l</td>
<td>8.5 ± 2.8</td>
<td>10.4 ± 2.2</td>
<td>0.032*</td>
</tr>
<tr>
<td>Total leucocyte count x10^9/l</td>
<td>17.8 ± 4.8</td>
<td>12.5 ± 7.7</td>
<td>0.078</td>
</tr>
<tr>
<td>Platelet count x10^9/l</td>
<td>172.5 ± 78.3</td>
<td>439.3 ± 78.6</td>
<td>0.044*</td>
</tr>
<tr>
<td>Total bilirubin mg/dl</td>
<td>7.1 ± 5.6</td>
<td>3.7 ± 6.6</td>
<td>0.041*</td>
</tr>
<tr>
<td>Aspartate transaminase (AST; IU/l)</td>
<td>149.7 ± 73.4</td>
<td>121.1 ± 42.3</td>
<td>0.006*</td>
</tr>
<tr>
<td>Alanine transaminase (ALT; IU/l)</td>
<td>96 ± 25.5</td>
<td>43.3 ± 25.6</td>
<td>0.036*</td>
</tr>
<tr>
<td>Alkaline phosphatase (SAP; IU/l)</td>
<td>326.8 ± 54.6</td>
<td>233 ± 59.1</td>
<td>0.074</td>
</tr>
<tr>
<td>INR</td>
<td>1.8 ± 0.9</td>
<td>1.36 ± 0.69</td>
<td>0.546</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>1.9± 0.69</td>
<td>2.12 ± 0.54</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.89 ±0.9</td>
<td>1.2 ± 0.48</td>
<td>0.229</td>
</tr>
<tr>
<td>Need for percutaneous drainage (n,%)</td>
<td>15 (53.3%)</td>
<td>10 (41.6%)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>9.6 ± 2.6 days</td>
<td>2.4 ± 7.2 days</td>
<td>0.076</td>
</tr>
<tr>
<td>Shock (n,%)</td>
<td>5 (17.8%)</td>
<td>0</td>
<td>0.036</td>
</tr>
<tr>
<td>Acute kidney injury (n,%)</td>
<td>4 (14.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SOFA score</td>
<td>3.9 ± 3.6</td>
<td>2.1 ± 1.4</td>
<td>0.078</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>12.8 ± 4.3</td>
<td>5.4 ± 3.6</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Abbreviations: SOFA, sequential organ failure score; APACHE II, acute physiology and chronic health evaluation score; INR, international normalized ratio.

We cultured Klebsiella pneumoniae and E coli from the pus aspirate in 2 patients each as secondary infections. The evaluation of liver enzymes (75%). Ultrasound findings showed a single liver abscess in 10 (35.7%) patients, and multiple abscesses in the other 18 (64.2%) (Figure 1). Ten patients also had peri-hepatic fluid, and pleural effusion (33.3%) on the ultrason. Doppler ultrasound revealed an eccentric right hepatic vein thrombus in 6 (21.4%) subjects but no evidence of hepatic vein outflow tract obstruction was noted. The mean size of the largest abscess was 7.2 ±2.8 cm. Contained rupture was seen in 4 (12.5%) patients only. Computed tomography (CT) scan confirmed the findings on ultrasound. In the typical case, arterial-phase contrast-enhanced CT scan showed a hypo-attenuating lesion with enhancing thickened walls due to hyperaemia (the double target sign) (Figure 2). Stool microscopy was positive in 10 (35.7%) for trophozoites or cysts of E histolytica. Serology was positive in all 28 subjects. When these subjects developed bleeding per rectum, all were noted to have fresh blood mixed with stools with passage of mucus. Five patients developed hemodynamic instability secondary to the colonic bleed, and required transient ionotropic support and blood transfusion with packed red blood cells. These 2 patients also had a prolonged prothrombin time and required thromboelastography based coagulopathy correction with fresh frozen plasma and cryoprecipitate. Percutaneous aspiration was done in 15 (53.5) subjects, and percutaneous drains were placed using ultrasound guidance, for 14 patients with multiple abscesses, which showed the characteristic anchovy sauce appearance, but did not reveal any active trophozoites. We cultured Klebsiella pneumoniae and E coli from the pus aspirate in 2 patients each as secondary infections.
In contrast, the patients who had only hepatic amoebiasis, had a much more favourable course requiring single time aspiration in 10 cases only. The sequential organ failure assessment score, (SOFA; 3.9 ± 3.6 vs. 2.1 ± 1.4, p=0.07), and the Acute Physiology and Chronic Health Evaluation (APACHE II; 12.8 ± 4.3 vs. 5.4 ± 3.6, p=0.046) were higher in those with synchronous disease than those with ALA alone. Up to 17.8% and 14.2% of patients with synchronous amebic liver and intestinal involvement had acute kidney injury and shock respectively, reflecting systemic sepsis. Three patients who presented with shock met criteria for toxic colitis, but were managed successfully with medical treatment or drainage of the liver abscess alone.

**Endoscopic and pathological evaluation**

On colonoscopy, ulcers were noted in the ileocaecal area in 21 patients and sigmoido-rectal area in 3 patients.

The ileal ulcers were serpiginous, with distinct raised, thickened, often undermined edges and erythematous indurated margins, haemopurulent exudates, and necrotic slough. Four had an adherent clot, which on washing revealed a visible vessel in the base of the ulcer. Active bleeding was noted in 18 patients, which was controlled initially with dilute epinephrine injection (1:1000). In cases with a visible vessel, we placed haemoclips at the site to control ooze (Figure 3). For patients with ooze from the ulcer margins, we used argon plasma coagulation (APC) to control the bleed. Sometimes two sessions were required to control bleeding, but all were managed successfully by endoscopic therapy alone. One patient had sigmoidorectal ulcers, which had ooze from the ulcer margins, and underwent a single session of APC to control the bleeding. As mentioned earlier, one patient had a large ulceroproliferative growth in the rectum with friable overlying mucosa, and superficial bleeding which appeared to be a malignant lesion on colonoscopic evaluation (Figure 4). The mass was biopsied and sections showed a base formed by fibrin and few degenerating cells. Beneath it there was granulation tissue composed of few blood vessels and mild inflammation. A few trophozoites of E histolytica were observed in the ulcer base, and showed haemophagocytosis.

**Differential Diagnosis**

- Tuberculosis
- Inflammatory bowel disease
- Colonic carcinoma with liver metastases.
- Pyogenic liver abscess
- Infected hydatid cyst
Treatment

All subjects received 2 weeks of oral or intravenous metronidazole in a dose of 2.4 gm per day in 3 divided doses. In addition, iv ceftriaxone or cefepime in a dose of 4 gm per day in two divided doses were given for ten days, for treatment of secondary infections as all the patients presented in a toxic state with complicated abscesses. The rectal mass due to the amoeboma disappeared after treatment with metronidazole for 2 weeks. Repeat colonoscopy did not reveal any abnormality in the 28 patients with ileocaecal ulcers and only residual erythema in the patient with the rectal amoeboma. Aspiration improved symptoms like fever, pain and breathlessness, but did not shorten the duration of hospital stay or duration of antibiotic therapy. The ALA resolved completely in all 28 cases. Colonic ulcer bleeds were controlled endoscopically, and a repeat colonoscopy 3 months later showed a complete resolution of the ulcers (Figure 5).

Discussion

It is generally considered that amoeboma formation occurs due to untreated or partially treated amoebic colitis and occurs in patients with chronic persistent infection.11 However, in the present report, only one patient had a prior history of symptoms or had received anti-amoebic treatment in the past. Moreover, all of them had evidence of ALA at the time when they were found to have colonic ulcers, suggesting that amoeboma formation can occur even in the acute phase of infection with simultaneous liver and bowel inflammation.4 Nevertheless, up to 50% of patients have been found to exhibit colonic ulceration on colonoscopy. Jaundice is noted in just 24% cases, as hepatic function remains largely unaffected in the majority of cases with ALA.13 Signs of liver cell failure such as jaundice, hypoalbuminemia and encephalopathy are caused by loss of viable hepatic parenchyma due to necrosis by the amoebae, and therefore are only seen in patients with large abscess volume or multiple abscesses.

Radiological imaging in amebiasis

On ultrasonography, an ALA is visualised as a focal hepatic lesion, which is single in 60% of cases and is most commonly located in the posterior superior part of the right lobe of the liver, classically involving segment VIII of the liver. The abscess is usually hypoechoic as compared with the normal liver parenchyma with fuzzy margins. In the center of the ALA, hyperechoic content may be seen. After completion of treatment with metronidazole or related compounds, the lesion tends to become more hypoechoic, and the margins become clearer due to waning off of the inflammation. Computed tomographic (CT) findings of Caecal amoeboma with and other colonic presentations has also been described as a mimicker of colonic malignancy.12 The ileocaecal valve is classically indurated with involvement of the mesentery and enlarged loco regional lymph nodes in the pericolonic area. The differential diagnoses for this clinical scenario include tuberculosis, lymphoma, actinomycosis, inflammatory bowel disease or even colonic cancer.12,14,15 Therefore a diagnosis of ameboma can only be one of exclusion, after eliminating more sinister diseases on histological examination of multiple biopsies obtained during colonoscopy.16 In a recent series, Misra et al reported that 55% of patients with ALA had colonic ulcers, including 90% of cases with and 41% in cases without diarrhoea at presentation. Although in the present series, we encountered a bleeding rectal amoeboma, the more common site for this lesion is the caecum.14 The frequency of colonic ulcers is clearly higher in patients with active diarrhea at presentation, as this would imply concurrent infection in the liver and intestine with shedding of amoebae (trophozoite or cyst forms) in the stools. Dysentery is rare in such cases, and the patients may well be asymptomatic cyst passers. In a meta-analysis of 310 patients with ALA, needle aspiration + metronidazole versus drug therapy alone produced similar benefit. Therefore there is little evidence to support or refute the practice of aspiration in order to hasten clinical recovery.17 This has to be done in cases with severe progressive or high risk disease, such as a subcapsular location with possibility of pericardial or peritoneal rupture, large left lobe abscess, secondary sepsis or in the case of non response to drugs alone.18 Risk factors for mortality include volume of abscess > 500ml, and signs of liver cell failure like encephalopathy, deepening jaundice (serum bilirubin >3.5 mg/dl) or hypoalbuminemia (serum albumin <2 gm/dl).14,19

Endoscopic and intervention radiological management of bleeding colonic ulcers

Endoscopic management of bleeding colonic ulcers is tricky as the exact site may be difficult to localize in the presence of clots and slough. The armamentarium of endoscopic techniques include, epinephrine injection (1:10,000 dilution), application of haemoclips, heat cautery, and argon plasma coagulation (APC), alone or in combination. Hemostatic clip placement offers the advantage of less injury to the mucosa and adjacent tissues compared to coagulation therapy, but in case of active bleeding and no visible vessel, APC may help provide superficial hemostasis.20 If an arterial source is suspected, urgent angiography and coil embolization is indicated to control massive bleeding, as this is difficult to control endoscopically. The feeder vessel is identified on computed tomographic angiography or digital subtraction angiography as an arterial blush at the site of the bleed. The vessel is selectively cannulated and microcoils or gelfoam are deployed to embolize the vessel.21 Severe lower gastrointestinal bleed is defined as

- Continued bleeding within the first 24 hours of hospitalization,
- Transfusion requirement of at least 2 units of packed red cells
- Decrease in the haematocrit value of 20% or more
- Recurrent bleeding after 24 hours of stability
- Need for multiple blood transfusion to maintain hemoglobin level despite adequate endotherapy22

Toxic colitis is a rare and severe complication. It is defined by (1) radiographic evidence of colonic dilatation; (2) Three or more of the following clinical findings: fever (>38.6°C), tachycardia (>100 beats/min), leucocytosis (>10.5×10^6 cells/μL) or anaemia; and (3) any of the following symptoms: dehydration, encephalopathy, electrolyte abnormalities, or refractory shock.

In refractory cases emergency hemicolecotomy is still necessary, but the procedure still has high mortality.
risk. The current indications for emergency surgery include
- A poor response to medical treatment with overwhelming sepsis
- Perforation of the colonic ulcers
- Intra-abdominal abscess or collection not responding to catheter drainage, and
- Presence of peritonitis

Usually, the clinical prognosis for amoebic toxic colitis is dismal with a mortality rate of nearly 40 to 70% in various reported series. Ishida et al reported that conservative surgery (e.g., colostomy or ileostomy without resection) leads to a mortality rate of around 80%, while radical surgery (e.g., hemicolectomy or total colectomy) reduces the mortality rate to 55%.

**Conclusion**

The clinical presentation of amoebiasis is varied, and remains a clinical conundrum in the present era. The synchronous presentation of amoebic liver abscess and intestinal disease has been described in our series with emphasis on medical treatment with timely antibiotics, effective radiological intervention, and most importantly judicious endoscopic management of bleeding in colonic disease to avert the need for emergency surgery. Thus we are able to report excellent results even in what would be considered fulminant colitis. In our patients, the most common manifestations were fever, jaundice, diarrhea or hematocchezia. Evaluation reveals synchronous hepatic and intestinal disease in 53% of patients with amebiasis.

**Take home message**

- There are four clinical forms of invasive intestinal amoebiasis, all of which are generally acute: dysentery or diarrhea, fulminant colitis, and localised proliferative growth known as amoeboma of the colon
- Synchronous amoebic liver abscess and colonic ulcers are more common than reported, as these are frequently asymptomatic.
- **Endoscopic management of bleeding colonic ulcers** is challenging and requires a combination of techniques such as epinephrine injection, application of haemoclips, heat cautery, or argon plasma coagulation (APC).
- In case of endoscopic failure, microcoil embolisation of the feeding vessel or even emergency surgery is necessary.

**References**