Cholestasis in amoebic liver abscess

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SUMMARY Two hundred and thirty six patients with amoebic liver abscess were investigated for cholestasis, its mechanism and the natural course of the disease. Cholestasis was seen in 29% of cases and it presented with some unusual features: it was frequently seen in young men (mean age 38.6 ± 6.3 years) (87%) with acute onset (69%) and was associated with signs of peritonism, or peritonitis (28%), splenomegaly (12%) and hepatic encephalopathy (coma 13%). Raised diaphragm was seen only in 37% of cases. Alcoholism may have contributed to the cholestasis in 37% of cases. Multiple (43%) and single (32%) large liver abscesses, especially on the inferior surface of the liver (25%), were common in jaundiced patients with amoebic liver abscess, while size and number of abscesses were directly related to the raised serum bilirubin concentrations. Bromsulphalein excretion (BSP) was found to be significantly reduced ($p < 0.01$) in patients with jaundice (60%). Retrograde injection of contrast media into the common bile duct during six necropsies showed compression by amoebic liver abscess on the hepatic ducts. The mortality (43%) and the complications were significantly higher ($p < 0.001$) in patients with jaundice. The aspiration/surgical drainage of amoebic liver abscess together with a combination of metronidazole and di-iodohydroxyquinoline was more effective than either metronidazole alone, or dehydroemetine with chloroquine.

Amoebiasis in its various forms is common in India. Among extra-intestinal amoebiasis the most frequently seen is hepatic amoebiasis.¹⁻³ Jaundice in amoebic liver abscess is unusual and if present, is mild.⁴⁻⁵ A varying incidence of jaundice in amoebic liver abscess has been reported.³⁻⁶⁻⁹ The mechanism of jaundice has not been properly investigated and various hypotheses have been put forward. The traditional explanation has been secondary infection of amoebic liver abscess, or pressure of an abscess on hepatic ducts,⁷⁻⁹⁻¹⁰ while other views are that the jaundice is parenchymal, or cholestatic in nature.⁸⁻¹¹⁻¹² It is a treatable medical emergency and a syndrome hitherto not well appreciated.

In this study, the incidence, clinical manifestations, and mechanism of jaundice in amoebic liver abscess are discussed.

Methods

PATIENTS

During the last 11 years 236 cases of amoebic liver abscess were investigated. Address for correspondence: Dr Pranesh Nigam, Type-IV/Block-7/No-2, BRD Medical College Campus, Gorakhpur 273013, India.

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abscess have been studied, and these were diagnosed according to the following criteria:²⁻³⁻¹³⁻¹⁴ (1) An enlarged tender liver, or tenderness over liver area. (2) Suggestive radiological findings particularly in the postero-anterior and lateral view of a chest radiograph. (3) Demonstration of amoebic pus, possibly containing trophozoites. (4) Serological evidence of amoebiasis (indirect haemagglutination test), and (5) Response to antiamoebic therapy.

A detailed proforma was used for recording clinical and laboratory data. Jaundice was confirmed by raised serum bilirubin of more than $17 \mu\text{mol/l}$. All patients had routine laboratory investigations together with a chest radiograph, liver function tests, sigmoidoscopy, and indirect haemagglutination test.¹⁵⁻¹⁶ When aspirated, abscesses were injected with air to visualise the cavity and follow progress.³⁻¹⁷ Liver biopsy and necropsy were done whenever possible.

All patients were allocated randomly three regimes: regime I: 65 cases received a combination of metronidazole (200 mg) and di-iodohydroxyquinoline (250 mg) two tablets of each tds for two

weeks or longer as indicated; regime II: 65 cases received metronidazole alone 1200 mg/day in three equally divided doses for two weeks or longer, as indicated; regime III: 106 patients received dehydroemetine 30 mg on the first day and then 60 mg daily for the next 10 days and/or chloroquine (base) 300 mg twice daily for two days then 150 mg twice daily for 19 days.

Aspiration and/or surgical drainage of liver abscesses (100 cases) was done if patients did not respond to treatment within four days and/or if severe localised pain, tenderness and repeated rigors persisted.

All patients were followed for four weeks and therapeutic response was graded into (WHO Criteria 1969). (1) Cure or good: complete remission of symptoms and signs, liver regressed to normal size, with biochemical and radiological improvement. (2) Probable failure: patients improved clinically, but biochemical and radiological abnormality persisted. (3) Failure or poor: no improvement clinically, radiologically, or biochemically.

The clinical, operative, biochemical, and necropsy data available in these patients are analysed in this paper.

Results

Two hundred and thirty six cases were studied and grouped into: group I: 68 patients with serum bilirubin more than 17 $\mu\text{mol/l}$. Group II: 168 cases

with serum bilirubin up to 17 $\mu\text{mol/l}$.

The incidence of jaundice in the present series was 29%. Age ranged from 12–68 years (mean 38.6 ± 6.3 years). The illness was more frequently seen in the third (28%) and fourth (46%) decades of life with male to female ratio of 4.7:1. The onset was usually gradual, but sudden onset (within 30 days) of the disease with rigors and sweating was noted in Group I (Table 1). Some patients (37%) drank about 100–200 ml alcohol (country liquor or whisky) per day for more than two years. Fever was usually intermittent (87%) and highest temperature recorded was 40°C in eight patients. Pain over the liver was usually of a dull aching type, but eight patients in group I had sharp stabbing pain. In 19 cases the pain (28%) was referred to the right shoulder and was affected by breathing and coughing. Splenomegaly was recorded in only 12% of group I patients, while 31% of patients had marked tenderness over the liver area and 26% had swelling in the epigastrium with bulging of the intercostal spaces. These findings were less frequently seen in group II.

Mild anaemia was present in 57% of cases, with leucocytosis varying from 11 000/mm³ to 14 600/mm³ in 46% of cases, with polymorphs predominating. The usual finding of raised and restricted movement of right dome of diaphragm was seen only in 37% of group I.

Serum bilirubin varied from 27.2–425 $\mu\text{mol/l}$. There was a significant rise in the conjugated fraction. Bromsulphalein was given to 20 cases in

Table 1 Clinical features

	Group I (n=68)	Group II (n=168)
1 Present history of amoebic dysentery	35 (57%)	127 (76%)
2 Past history of amoebic dysentery	47 (69%)	134 (80%)
3 History of alcohol ingestion	22 (37%)	23 (14%)
4 Jaundice	62 (91%)	—
5 Sudden (within 30 days) onset with rigors and sweating	47 (69%)	23 (14%)
6 Intermittent pyrexia up to 40°C	59 (87%)	126 (76%)
7 Pain over liver area: dull aching	39 (57%)	134 (80%)
sharp stabbing	8 (12%)	9 (5%)
referred to right shoulder and accentuated by respiration	19 (28%)	16 (9%)
severe	21 (31%)	19 (11%)
8 Hepatomegaly: with tenderness	45 (66%)	154 (92%)
marked tenderness	21 (31%)	9 (5%)
9 Visible swelling in epigastrium and/or bulging of intercostal spaces	18 (26%)	18 (11%)
10 Splenomegaly	8 (12%)	9 (5%)
11 Signs of peritonism and/or peritonitis	19 (28%)	6 (4%)
12 Respiratory signs: right lower zone consolidation	8 (12%)	9 (5%)
right pleural effusion	11 (16%)	7 (4%)
13 Hepatic encephalopathy (coma)	9 (13%)	—
14 Routine investigations: Haemoglobin <10 g/dl	39 (57%)	71 (42%)
Leucocytes > 10 000/mm ³	31 (46%)	61 (36%)
Raised right dome of diaphragm	22 (37%)	134 (80%)

group I and 30 patients in group II. Bromsulphalein was retained more than 10% in 30 seconds in 60% cases in group I, but only in 17% cases in group II. Bromsulphalein excretion was significantly reduced ($p<0.01$) in group I patients. Liver enzymes were increased and serum albumin decreased more in group I compared with group II patients (Table 2).

Site, size, and number of abscess cavities were determined by air replacement studies,^{3 17} at necropsy, or at open surgical drainage (Table 3). An abscess of more than 5 cm diameter, or from which more than 125 ml of pus was aspirated was termed large.^{3 6} Single abscess cavities were more frequent in patients without cholestasis (group II=80%), while in group I abscesses situated over the inferior surface of the liver were more frequently associated with jaundice (25%). The level of serum bilirubin was directly related to the size and number of abscess cavities (Table 4).

On histopathological examination amoebae could be seen in the necrotic liver tissue and abscess wall. At necropsy (six cases) contrast was injected into the common bile duct in retrograde direction, and showed distortion and compression of the hepatic biliary tree by large liver abscesses in the lower part of the liver.

The overall mortality in the present series of 236 cases was 23%. Mortality was significantly higher ($p<0.001$) in group I (43%) compared with group II (16%). Table 5 compares the mortality and complications in the two groups.

Table 6 gives the comparative results of the different treatments. The combination of metronidazole and di-iodohydroxyquinoline was most satisfactory and 91% of patients responded (regime I). The mortality was significantly lower (8%) with this regime, than with the alternatives (regime II=14%, regime III=39%). The time to recovery was also shortest with regime I and there were fewer unwanted effects. Patients on dehydroemetine and/or chloroquine (regime III)

experienced more unwanted effects (47%), compared with patients who received metronidazole either alone (regime II=22%), or in combination with di-iodohydroxyquinoline (regime I=12%). Unwanted effects in patients on regime III were nausea and vomiting (42%), abdominal cramps (15%), weakness (39%), muscle pains (24%), tachycardia (38%) and hypotension (38%) with electrocardiographic changes (24%) comprising T wave inversion (13%) and prolongation of QTc interval (10%). Patients on metronidazole either alone, or in combination, usually experienced a metallic taste and nausea with, or without vomiting.

Aspiration and/or surgical drainage of liver abscesses was done in 100 cases and results are shown in Table 6. There was a fall in the serum bilirubin in 35 to 40 patients with jaundice amounting to almost 50% of the initial bilirubin concentration within a week. Mortality was significantly lower in aspirated patients (11 out of 40 patients) as compared with others.

Discussion

Amoebiasis is well known for its protean manifestations and can stimulate many diseases in tropical countries. Commonest is hepatic amoebiasis among extra-intestinal amoebiasis. In such cases hyperbilirubinaemia has been reported but its incidence and severity is variable.^{6-9 12 17} We observed hyperbilirubinaemia in 68 out of 236 cases (29%) of amoebic liver abscess, similar to that reported by Kamat *et al*¹⁷ Joshi *et al*⁶ and Dutta *et al*.¹⁸

Various studies emphasise the difference in life history of patients of amoebic liver abscess with, or without jaundice. Patients with amoebic liver abscess and jaundice had an acute onset of disease with rigors and sweating (69%). Adult young men most frequently had an acute onset (87%). Barbour and Juniper⁴ and Nigam *et al*^{2 3} observed an acute

Table 2 Liver function tests

	Group I (n=68)	Group II (n=168)	χ^2 (df=1)	
Aspartate transaminase >0.6 $\mu\text{mol/l}$	39 (57%)	3 (2%)	81.2	$p<0.0001$
Alanine transaminase >0.86 $\mu\text{mol/l}$	46 (68%)	3 (2%)	123.5	$p<0.0001$
Alkaline phosphatase >0.20 U ³	45 (66%)	5 (3%)	112.1	$p<0.0001$
Prothrombin time >15 seconds	25 (37%)	5 (3%)	49.6	$p<0.0001$
Serum protein <5 g/dl	45 (66%)	61 (36%)	16.2	$p<0.001$
Serum albumin < g/dl	39 (57%)	52 (31%)	13.1	$p<0.001$
Reversal of albumin/globulin ratio	41 (60%)	55 (33%)	14.5	$p<0.001$
Thymol turbidity >5 units	39 (57%)	9 (5%)	53.2	$p<0.0001$
Bromsulphalein test positive	12 (60%)	5 (17%)	8.2	$p<0.01$

Bromsulphalein test done in group I=20 and group II=30 patients. BSP retention >10% in 30 seconds=positive test.

Table 3 Site, size and number of liver abscess cavities

	Group I (n=40)	Group II (n=60)
I Size and number: 1 Single: Large	13 (33%)	10 (17%)
Moderate	6 (15%)	17 (28%)
Small	4 (10%)	21 (35%)
2 Multiple: Large	9 (23%)	4 (7%)
Moderate	5 (13%)	3 (5%)
Small	3 (7%)	5 (8%)
II Site: 1 Right Lobe: Superior	14 (35%)	40 (67%)
Inferior	10 (25%)	5 (8%)
Central	6 (15%)	7 (12%)
Lateral	6 (15%)	6 (10%)
2 Left Lobe	2 (5%)	2 (3%)
3 Extensive	2 (5%)	

onset in men of 30–50 years. Amoebic dysentery is present in a small number of patients and past history of dysentery is said to be rare,^{4 13} but in the present series and in our previous studies^{1–3} most (57%) patients had a present, or past history of amoebic dysentery. Excess alcohol consumption was significantly higher ($\chi^2=11.17$, $p<0.001$) in group I (37%) compared with group II (14%) patients. Alcoholism has been regarded for a long time as predisposing to amoebic liver abscess and pain. The incidence of jaundice is also higher in alcoholics suffering from amoebic liver abscess.¹⁹ This is not surprising as alcohol can induce alcoholic hepatitis and cholestatic jaundice.^{13 20 21}

The rise in serum bilirubin varied from 27.2–425 $\mu\text{mol/l}$. The important finding observed was a significant rise in the conjugated fraction. The hyperbilirubinaemia may be the result of: (1) Increased load of bilirubin. (2) Decreased hepatic uptake. (3) Decreased conjugation and (4) decreased excretion of bilirubin.

Dutta *et al*^{9 22} tried to explain the mechanism of hyperbilirubinaemia (cholestasis) in amoebic liver abscess. Bromsulphalein and bilirubin have different metabolic pathways in hepatic cells. In patients with amoebic liver abscess the transport maximum, which represents rate of BSP excretion

by hepatic parenchymal cells, was significantly reduced. Storage capacity, however, was well preserved. These changes occur with or without jaundice and are unlike those in hepatitis, where storage capacity is reduced.^{7 13} These findings are compatible with biochemical changes seen in obstructive jaundice. In the present series the BSP test was abnormal and liver function was impaired to a minor degree, which could be because of prolonged cholestasis. The hypoproteinaemia and hypoalbuminaemia (57%) seen in group I patients might be caused by poor nutrition, while raised serum transaminases concentrations could also be expected, because of injury and death of hepatocytes.

With the studies of BSP, glutathione conjugating enzyme (cytoplasmic enzyme), uridine 5-diphosphate glucuronyl transferase (microsomal enzyme) and chromium labelled red cell survival (normal), it became clear that jaundice in amoebic liver abscess patients is not because of increased load and decreased hepatic conjugation.^{7 9 18 22} Excretory pathway, however, is defective as shown by BSP excretion studies.⁹ This was also observed in the present series. A compression effect of amoebic liver abscess on bile ducts was seen in six necropsies.

Tables 3 and 4 emphasise three important points:

Table 4 Correlation of size and number of abscess with serum bilirubin concentrations (Group I=40 cases).

Size and number of abscess cavities	Cases (no)	Serum bilirubin in $\mu\text{mol/l}$	
		Range	Mean
I Single: Large	13 (33%)	238–391	312.8
Moderate	6 (15%)	142.8–258.4	198.9
Small	4 (9%)	27.2–180.2	107.1
II Multiple: Large	9 (23%)	244.8–425	345.1
Moderate	5 (13%)	142.6–275.4	207.4
Small	3 (7%)	30.6–149.6	115.6

advisable if abdominal complications are likely and such an approach has given very encouraging results in the present series.

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