



Review

ACUTE ACALCULOUS CHOLECYSTITIS AN UNUSUAL PRESENTATION OF DENGUE FEVER

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ARTICLE INFO

Article History:Received 17th September, 2022Received in revised form 27th September, 2022Accepted 20th October, 2022Published online 28th October, 2022**Key words:**

Dengue Fever, Dengue, Acalculous Cholecystitis, Acute Acalculous Cholecystitis

ABSTRACT

Background: Dengue Fever is a self-limiting arboviral infection characterised by fever, headache, myalgia, rash, nausea, and vomiting. A main feature of severe dengue is capillary leakage of which acalculous cholecystitis is considered as an atypical presentation. **Aims and Objectives:** To study the prevalence of Acute Acalculous cholecystitis and its correlation with the severity of dengue fever. **Materials and Method:** Serologically confirmed 540 cases of dengue fever who were hospitalized were included in the study. Detailed clinical examination, various laboratory parameters viz. Complete blood count, coagulation profile, biochemical investigations (renal function test and hepatic function test), and ultrasound of the abdomen were done. Patients were followed up from admission to discharge or death. Data was analysed with the statistical package SPSS 1.0.0.1406. The Chi-square test was used for the analysis of variables. P-value of <0.05 was considered significant. **Observations:** This study included 540 patients with a male and female ratio of 1.07:1. Patients presented with acute abdomen with or without complications like Shock, DHF, Hepatic or Renal dysfunction, and/or multiorgan dysfunction. Acalculous cholecystitis was observed in 39.6 % of cases (n=214). **Conclusion:** Acute cholecystitis occurred in a significant proportion of patients with dengue fever and this complication should be considered alarming in endemic areas.

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INTRODUCTION

Dengue Fever is a self-limiting arboviral infection caused by the bite of *Aedes aegypti* mosquito. Dengue fever is characterised by fever, headache, myalgia, rash, nausea and vomiting. A few patients may develop dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and acute abdomen which could be life-threatening if not managed properly. The crux in the management of dengue fever is judicious intravenous fluid therapy and correction of thrombocytopenia. Timely management decisions have proved critical in the positive outcome for patients. A very short gap between the onset of hemorrhage and death, especially in young children makes the management of dengue fever a challenge and is a critical factor for survival. Successful management of dengue fever depends upon early recognition of symptoms and judicious fluid management. Development of DHF/DSS occurs due to the lysis of platelets by anti-platelet antibodies and anti-endothelial antibodies. Further complement activation and capillary leakage due to endothelial damage causes pleural, peritoneal, and pericardial effusion and pericholecystic fluid collection.

Various atypical manifestations of dengue virus infection have been reported including fulminant hepatitis, encephalopathy,

cardiomyopathy, acute pancreatitis and acalculous cholecystitis [3, 8, 12] Frequent sonographic findings in a case of dengue include thickened gall bladder with pericholecystic fluid, ascites, splenomegaly and pleural effusion which is commonly right sided. [14, 15, 16]

MATERIAL AND METHOD

During a period of 4 months from July 2021 to November 2021 an observational study was conducted after receiving informed consent from participants. A total of five hundred and forty (n=540) serologically confirmed dengue fever patients who were hospitalized were included in the study. IgM anti-dengue antibodies using the IgM antibody capture enzyme linked immunosorbent assay (MAC-ELISA) according to national vector borne disease control programme (NVBDCP) guidelines for diagnosis of dengue fever, was done. Patients were followed up from admission to recovery or death. The criterion for admission was acute febrile illness with duration of 2-7 days and positive serology for dengue infection. Patients presented with fever, persistent vomiting, dehydration, inability to tolerate oral fluids, severe pain in abdomen, hypotension, inappropriate tachycardia with fever, hemorrhagic manifestations like petechiae, purpura, oral mucosal bleed, upper gastrointestinal bleeding, bleeding from

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infection sites, serous fluid accumulation (Pleural, Pericardial, and Peritoneal), renal failure, organ impairment and thrombocytopenia. Patients positive with infections like Typhoid, Malaria, or any other infection with or without thrombocytopenia were essentially excluded.

Detailed clinical examination was done at admission and blood samples were collected for hematological, coagulation profile and biochemical investigations for hepatic and renal functions. Ultrasound of abdomen and X-ray chest was also done.

Ethical Clearance was taken from Ethical Committee of F. H. Medical College, Etmadpur, Agra, U.P.

Statistical Analysis was done using IBM SPSS Version 1.0.0.1406, Chi-Square was used for analysis and P-value of <0.05 was considered significant.

RESULT

A total of 540 patients (279 female and 261 male) with dengue fever were studied. The mean age of the patient was 33 ± 13.5 years. The duration from onset of fever to the first hospital visit was 4.2±0.9 days (i.e. ranging from 3 to 6 days).

Fever was the most prevalent presenting complaint of the patients, with 100% prevalence. It was followed by myalgia (85.9%), headache (66.1%), abdominal pain (45%), arthralgia (24.8%), bleeding manifestation (18.8%), and retro-orbital pain (15%), as the presenting complaints of the patient. [Table 1]

Table 1 Clinical presentation of Dengue Patients at the time of admission

Clinical Presentation	Total Number of Patients (n=540)	Patients with acalculous cholecystitis (n=214)	Patients without cholecystitis (n=326)
Fever	540 (100%)	214 (100%)	326 (100%)
Myalgia	464 (85.9%)	203 (94.8%)	261 (80%)
Headache	357 (66.1%)	191 (89.2%)	66 (20.2%)
Pain abdomen	243 (45%)	175 (81.7%)	68 (20.8%)
Arthralgia	134 (24.8%)	57 (26.6%)	77 (23.6%)
Bleeding Manifestation	102 (18.8%)	84 (39.2%)	18 (5.5%)
Retro-Orbital Pain	81 (15%)	26 (12.1%)	55 (16.8%)
Shock	29 (5.3%)	21 (9.8%)	8 (2.4%)
Pallor	14 (2.5%)	10 (4.6%)	4 (1.2%)
Icterus	5 (0.9%)	5 (2.3%)	0

Out of 540 patients, 102 patients had bleeding manifestations. Petechiae were present in 102 patients (18.8%) in combination with other bleeding manifestations like Malena (17.5%), Epistaxis (1.8%), fresh bleed per rectum (1.1%), gingival bleeding (0.5%), and Subconjunctival hemorrhage (0.1%). Bleeding manifestations were found more in patients with acalculous cholecystitis (39.2%) as compared to those without cholecystitis (5.5%) [Table 2] Out of 540 patients 75.9% were diagnosed with dengue fever, 18.8% with dengue haemorrhagic fever (DHF), and 5.3% with dengue shock syndrome (DSS). Of which, 84 patients with DHF and 21 patients with DSS had acalculous cholecystitis. Blood investigations included Complete blood count, dengue serology, liver function test, kidney function test, coagulation profile and Ultrasound of abdomen.

Table 2 Table of Patients with Hemorrhagic manifestations

Bleeding Manifestations	Total Patients with Dengue Fever (n=540)	Patients with Acalculous Cholecystitis (n=214)	Patients without Cholecystitis (n=326)
Petechiae	102 (18.8%)	84 (39.2%)	18 (5.5%)
Malena	95 (17.5%)	64 (29.9%)	31 (9.5%)
Epistaxis	10 (1.8%)	4 (1.8%)	6 (1.8%)
Fresh Bleed per rectum	6 (1.1%)	4 (1.8%)	2 (0.6%)
Gingival Bleeding	3 (0.5%)	1 (0.4%)	2 (0.6%)
Subconjunctival Hemorrhage	1 (0.18%)	0	1 (0.3%)

Table 3 the distribution of patients with Platelet Counts

Platelet Count (per microliter of blood)	Total Number of patients (n=540)	Number of patients with acalculous cholecystitis (n=214)	Number of patients without cholecystitis (n=326)
Platelet Count less than 1,00,000	201 (37.22%)	22 (10.2%)	179 (54.9%)
Platelet Count 20,000-50,000	241 (44.62%)	131 (61.2%)	110 (33.7%)
Platelet Count 10,000-20000	84 (15.56%)	50 (23.3%)	34 (10.4%)
Platelet Count less than 10,000	14 (2.60%)	11 (5.14%)	3 (0.9%)

The blood picture of all patients (n=540) showed thrombocytopenia (Table 3) and reduced total leucocyte counts on first visit to the hospital. Aminotransferases were deranged in majority of patients with dengue fever, with 79.4% patients having SGOT values above upper limit of normal and 60% with SGPT above upper limit of normal. [Table 4] The liver function tests showed that SGOT levels of 20.6% of patients were found to be normal (0-45 U/L), 46-100 U/L in 75.7% followed by severely deranged values of >100U/L in 3.7% of the patient population.

Normal SGPT levels (0-45U/L) were found in 40% patients, with 58% showing marginally raised levels of 46-100U/L and 2% patients had severely raise levels of >100U/L. Among the 214 patients with acute acalculous cholecystitis, 81.3% had deranged SGOT and 80% had deranged SGPT values. USG findings in dengue patients included Gall Bladder Edema (40.1%), Ascites (37%), Pleural effusion (24.2%), Hepatomegaly (10.5%), Splenomegaly (7.4%), and Cholelithiasis (0.5%) [Table 5] Out of 540 patients, 214 (39.6%) patients showed features of acalculous cholecystitis i.e. USG findings showed thickened gallbladder wall, a positive Murphy's sign, and no cholelithiasis, with or without pericholecystic fluid accumulation. In patients with acalculous cholecystitis (n=214), other USG findings were also observed which included ascites (93%), pleural effusion (49%), hepatomegaly (27%), and splenomegaly (17%).

All of the patients were given conservative treatment, responded well and recovered uneventfully.

Table 4 Liver enzymes in dengue patients

	Total Patients with dengue fever (n=540)	Patients with Acalculous Cholecystitis (n=214)	Patients without Cholecystitis (n=326)
SGOT			
0-45U/L	111 (20.6%)	60(28%)	51 (15.6%)
46-100U/L	409 (75.7%)	154(71.9%)	255 (78.8%)
>100U/L	20 (3.7%)	20(9.4%)	0
SGPT			
0-45U/L	216 (40%)	43(20%)	173 (53%)
46-100U/L	313 (58%)	160(74.8%)	153 (46.9%)
>100U/L	11 (2%)	11(5.2%)	0

Table 5 USG findings in dengue patients

Radiological Finding	Total patients with dengue Fever (n=540)	Number of Patients with Acalculous Cholecystitis (n=214)
GB Edema	217 (40.1%)	214 (100%)
Ascites	200 (37%)	198 (93%)
Pleural Effusion	131 (24.2%)	104 (49%)
Hepatomegaly	57 (10.5%)	57 (27%)
Splenomegaly	40 (7.4%)	37 (17%)
Cholelithiasis	3 (0.5%)	0

DISCUSSION

Dengue fever has a wide clinical spectrum ranging from mild asymptomatic presentation to life threatening situations. Management of dengue fever is simple and inexpensive but requires a prudent approach. Good clinical assessment and management decisions at the primary and secondary levels are critical in the outcome of patients.

Acute acalculous cholecystitis is defined as an acute inflammation of gallbladder in the absence of cholelithiasis. Acute acalculous cholecystitis presents with features of right hypochondrial pain, fever, and abnormal liver function tests [6]. A severe complication like acute acalculous cholecystitis in dengue fever is uncommon in India [6]. Acute acalculous cholecystitis is associated with a high mortality rate of upto 30% due to underlying severity of illness [4]. In our study, Acute acalculous cholecystitis was found in 39.6% of cases (n=214). Diagnostic ultrasound remains the imaging modality of choice with specificity of 100% [9]. Wu KL et al. [17] also reported thickened gallbladder wall, pleural effusion and ascites in ultrasonographic study. In our study, acute acalculous cholecystitis was also associated with Ascites (93%), Pleural Effusion (49%), Hepatomegaly (27%), and Splenomegaly (17%) (Table 5). These findings are consistent with previous studies [7, 10]. We also observed DHF in 84 patients and DSS in 21 patients along with acute acalculous cholecystitis, similar to previous studies [5, 13]

Laboratory findings usually associated with dengue fever are neutropenia, lymphocytosis, thrombocytopenia, and raised liver enzymes. We observed WBC 4200 ± 310 , platelet count $45000 \pm 32743 /\text{mm}^3$, AST 210 ± 110.4 IU/L, and ALT 310 ± 119 IU/L. Bhattys et al. [2] also observed similar findings in their study.

In our study, all patients (n=214) with acalculous cholecystitis had severe thrombocytopenia, higher levels of derangement of liver enzymes and directly correlated with severe dengue fever (P value <0.001).

Proposed hypotheses in the pathogenesis of acute acalculous cholecystitis are gallbladder mucosal injury due to stasis of bile, gall bladder ischemia due to multiple arterial occlusion and disruption of microcirculation, and finally, release of cytokines and pro-inflammatory eicosanoids resulting in inflammation and coagulation [1]. Although the exact cause of development of acute acalculous cholecystitis in dengue fever is uncertain, but the direct viral invasion of gallbladder may be responsible for edema and exudation [2].

The mean duration for hospital stay in our patients was 4.2 ± 0.9 days which is comparable to previous studies [11]. The usual treatment of acute acalculous cholecystitis in dengue fever requires conservative therapy and without surgical intervention. The conservative treatment includes proper clinical assessment, judicious intravenous fluid administration to maintain hydration, and transfusion of platelet concentrates if required. There is no role of prophylactic platelet transfusion. Although acute acalculous cholecystitis carries a high mortality rate but in our study, mortality was zero. Patients were managed conservatively and recovered uneventfully, without surgical intervention.

LIMITATIONS

In our study we found that some patients left the study midway due to financial constraints and some were unable to arrange platelet concentrates leading to further deterioration of patient condition. Also, this study was conducted over a short period of 4 months and only patients who stayed for the full course of treatment were included in the study.

CONCLUSION

Positive murphy sign, pain abdomen and sonographically proven acute acalculous cholecystitis in dengue fever should be considered as a warning sign. We inferred that patients presenting with acalculous cholecystitis in dengue fever had more severe thrombocytopenia, more derangement in liver enzymes and were more prone to develop severe dengue fever compared to dengue patients without acalculous cholecystitis. We found that acute acalculous cholecystitis associated with dengue fever seems to be a separate entity and should be managed conservatively without need for surgical intervention.

Financial support & Sponsorship: NONE

Conflicts of interest: NONE

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How to cite this article:

Mayank Butola et al., (2022). Acute acalculous cholecystitis an unusual presentation of dengue Fever. *International Journal of Current Advanced Research*, 11(10), pp.1631-1634. DOI: <http://dx.doi.org/10.24327/ijcar.2022.1634.0364>
