

Acalculous Cholecystitis in Dengue

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ABSTRACT

OBJECTIVE: To assess the incidence of acute acalculous cholecystitis in patients with dengue fever and assess its association with laboratory parameters.

METHODOLOGY: This cross-sectional study was conducted in Creek General Hospital, United Medical and Dental College, Karachi, Pakistan, from September 2020 to October 2021. Patients were included in the study through consecutive sampling. After their informed consent, all adult patients diagnosed with dengue fever, based on serological tests, were included in this study. Exclusion criteria were co-existing cholelithiasis, chronic liver disease, hemolytic and rheumatological disorders, metabolic syndrome, dyslipidemia, chronic kidney disease, use of oral contraceptive pills, pregnant females, enteric fever, vasculitis and recent surgery or trauma.

The ultrasonographic features of these patients were recorded along with other laboratory investigations. SPSS ver 23.0 was used to analyze the data. Student t-tests and Chi-square tests were used to assess the association between the variables, and a P-value of <0.05 was considered significant. **RESULTS:** 248 patients with dengue fever were included in this study. More than 49% of these patients were diagnosed to have acalculous cholecystitis. Development of this condition was significantly associated with hemoconcentration, thrombocytopenia, leucopenia and transaminitis. All the patients recovered with conservative management, but the duration of hospital stay for these patients was considerably higher than in those without this condition.

CONCLUSION: Almost half of the patients diagnosed with Dengue fever developed acalculous cholecystitis. These patients recovered with conservative management.

KEYWORDS: Dengue, acalculous cholecystitis, hemoconcentration, thrombocytopenia, leucopenia.

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INTRODUCTION

Dengue fever (DF) is a mosquito-borne disease with high mortality and morbidity¹. The incidence of dengue fever and dengue hemorrhagic fever (DHF) has increased thirty folds globally in the last four decades, and more than half the world's population (including developed countries) is now threatened with infection by the dengue virus². Dengue virus infection manifests with a wide range of severity, from mild febrile illness to life-threatening diseases like dengue hemorrhagic fever and dengue shock syndrome (DSS). Some unusual clinical manifestations have also been reported, including fulminant hepatitis, encephalopathy, cardiomyopathy, acute pancreatitis and acalculous cholecystitis³.

Acalculous cholecystitis classically has been reported with burns, trauma, total parenteral nutrition, vasculitis, post-surgical and ICU patients, and certain infections such as salmonellosis or cytomegalovirus in immunocompromised patients^{4,5}. It is associated with high mortality in these conditions⁶. Acalculous cholecystitis is now frequently observed in patients with dengue fever⁷.

Acalculous cholecystitis in DF is a feature of capillary leak syndrome. The development of this condition usually occurs in the critical phase of DF. It is essential to recognize this stage and initiate an appropriate and reasonable management protocol to prevent complications⁸. It is necessary to acknowledge severe and critical Dengue so that early replacement of fluid to ensure adequate intra-vascular volume and tissue perfusion is possible. This can prevent the development of dengue shock syndrome. Ascites, pleural effusion, and gall bladder edema from capillary leak syndrome are indicators of severe and critical Dengue. Ultrasound is a valuable tool to diagnose this stage early as it is more sensitive than clinical assessment. It has been demonstrated that clinical ascites were shown in 12.8% and pleural effusion in 9.9%. Yet, on ultrasonography, 44.5% of patients had ascites, 29.7% had gall bladder edema, and 14.8% had evidence of pleural effusion. Ultrasonography is highly sensitive in detecting even small amounts of pleural effusion and ascites. Ultrasonography could detect plasma leakage in various body compartments of the body. Ultrasonographic signs suggestive of plasma leakage were evident before significant hematocrit changes occurred. Therefore, during an epidemic, the ultrasonographic findings suggestive of gallbladder (GB) edema with or without collection of free fluid in other areas in a febrile patient should

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indicate the possibility of DF/DHF.

Research has shown differences in clinical and laboratory parameters between DF and DHF. The current need is to predict the development of DHF/DSS, which would provide information to identify individuals at higher risk and give clinicians sufficient time to reduce dengue-related morbidity and mortality. Lee et al., in their study, tried to derive a score from predicting Dengue's severity using simple, readily available and measurable parameters. Simple severe dengue risk scores could assist clinicians in deciding which dengue patients need hospitalization. They may improve clinical practice by decreasing the number of unnecessary hospitalizations and by reducing mortality and morbidity, particularly in resource-limited countries.

METHODOLOGY

This descriptive cross-sectional study was conducted at Creek General Hospital, United Medical and Dental College, Karachi, Pakistan, from September 2020 to October 2021. The patients were included in the study through consecutive sampling, and a sample size of 248 patients was calculated with a confidence level of 95%. The Institutional Review Board approved the study protocol. Each subject gave informed consent before being included in the study.

All patients 18 to 75 years of age and both genders diagnosed with Dengue fever were included in the study. Exclusion criteria were co-existing cholelithiasis, chronic liver disease, hemolytic and rheumatological disorders, metabolic syndrome, dyslipidemia, chronic kidney disease, use of oral contraceptive pills, pregnant females, enteric fever, vasculitis and recent surgery or trauma.

Dengue fever was diagnosed based on clinical presentation and confirmed through positive Dengue NS-1 antigen and a positive Dengue IgM antibody or a four-fold rise in Dengue IgG antibody for a late or convalescent phase blood specimen. Dengue NS-1 antigen was detected by immunochromatographic assay (Dengue NS1 Ag Strip (BioRad Laboratories)). Dengue IgM and IgG antibodies were assessed through ELISA. Complete blood analysis, liver function tests and coagulation profile were conducted for all subjects. All demographic data were recorded on a questionnaire. Abdominal ultrasound was performed in real-time for patients with abdominal pain, nausea or vomiting and abnormal results on liver function tests. The diagnosis of acute acalculous cholecystitis was made according to the clinical features and sonographic findings. Thickened gall bladder wall of > 3.5 mm, positive sonographic Murphy's sign, which is the maximum tenderness of a sonographically localized gall bladder and a gall bladder without stones, were considered consistent with acute acalculous cholecystitis⁹.

As required, the patients were managed

conservatively with antipyretics, intravenous fluids, antibiotics, and platelet or blood transfusion. Surgery was kept as an option only in patients not responding to conservative management. The outcomes of the patients were recorded as discharged or expired.

The data was entered and analyzed on SPSS 23.0. The continuous variables were computed with mean and standard deviation, while the categorical variables were calculated with numbers and percentages. The association between the variables and the presence of acalculous cholecystitis was assessed through Student's t-test and Chi-square test, and a P-value of <0.05 was considered statistically significant.

RESULTS

There were 248 patients diagnosed with dengue fever during the study period. The age ranged from 18 to 75 years with a mean of 28.7±11.1 years. 54% of the patients were male, and 46% were female. The laboratory investigations are given in the tables. (Table-I)

Acalculous cholecystitis was seen in 49.6 % of the subjects. (Table-I)

The mean duration of hospital stay for patients diagnosed with acalculous cholecystitis was 5.3±2 days as against 2.3±1.8 days for patients who did not have acalculous cholecystitis. The period of stay was significantly prolonged (p-value<0.05) in patients with this condition.

The presence of acalculous cholecystitis was associated significantly with hemoconcentration (p-value <0.05), leucopenia (p-value <0.05), thrombocytopenia (p-value<0.00) and deranged liver transaminases (p-value <0.00). (Table-II)

The patients diagnosed with acalculous cholecystitis recovered fully with the conservative management line. No surgical intervention was needed in any patient. (Table-I)

TABLE I: CHARACTERISTICS OF SUBJECTS

| Variable | Descriptive Statistics | |
|---|------------------------|-------------|
| Age (years) | 28.7±11.1* | |
| Gender | Male | 134 (54%) |
| | Female | 114 (46%) |
| Haemoglobin g/dl (at admission) | 13.8±2.2* | |
| Haemoglobin g/dl (at discharge) | 11.7±2.06* | |
| Hematocrit % (at admission) | 40.9±5.8* | |
| Hematocrit % (at discharge) | 34.4±6.3* | |
| Hemoconcentration | Yes | 94 (37.9%) |
| | No | 154 (62.1%) |
| Total leucocyte count x10 ³ /µl (at admission) | 3.98±1.9* | |
| Total leucocyte count x10 ³ /µl (at discharge) | 6.5±2.25* | |

| | | |
|--|------------|---------------|
| Leucopenia | Yes | 172 (69.4%) |
| | No | 76 (30.6%) |
| Neutrophil % (at admission) | | 54.1±10.7* |
| Platelet count x10 ³ /µl(at admission) | | 77.84±63.74* |
| Platelet count x10 ³ /µl (at discharge) | | 160.35±87.32* |
| Thrombocytopenia | Yes | 216 (87.1%) |
| | No | 32 (12.9%) |
| Transaminitis | Yes | 201 (81%) |
| | No | 47 (19%) |
| Outcome | Discharged | 246 (99.2%) |
| | Expiry | 2 (0.8%) |
| Acalculous cholecystitis | Yes | 123 (49.6%) |
| | No | 125 (50.4%) |

*Mean±SD

TABLE II: RELATIONSHIP OF ACALCULOUS CHOLECYSTITIS WITH DIFFERENT VARIABLES

| Variables | With Cholecystitis (123) | Without Cholecystitis (125) | P-Value | |
|---|--------------------------|-----------------------------|---------|--------|
| Age in years (mean±SD) | 28.5±10.3 | 28.9±11.9 | 0.76* | |
| Gender | Male | 66 | 68 | 0.9† |
| | Female | 57 | 57 | |
| Days of stay (mean±SD) | 5.3±2.0 | 2.3±1.8 | 0.00* | |
| Hemoglobin g/dl (mean±SD) | 14.0±2.3 | 13.5±2.0 | 0.08* | |
| PCV% | 41.5±6.1 | 40.3±5.5 | 0.1* | |
| Hemoconcentration | Yes | 66 | 86 | 0.005† |
| | No | 55 | 33 | |
| Total leucocyte count x10 ³ /µl (mean±SD) | 3.8±2.0 | 4.1±1.7 | 0.1* | |
| Absolute neutrophil count x10 ³ /µl(mean±SD) | 2.06±1.4 | 2.4±1.4 | 0.057* | |
| Leucopenia | Yes | 95 | 77 | 0.009† |
| | No | 28 | 48 | |
| Platelet count x10 ³ /µl (mean±SD) | 51.2±43.5 | 104.0±69.5 | 0.00* | |
| Thrombocytopenia | Yes | 117 | 99 | 0.000† |
| | No | 6 | 26 | |
| Transaminitis | Yes | 112 | 89 | 0.000† |
| | No | 11 | 36 | |

*t-test, † Chi-square

DISCUSSION

Dengue fever can present with a wide range of clinical manifestations. These can range from asymptomatic

to classic and dengue fever with complications that can be severe and life-threatening. Dengue infection usually presents typical features such as fever, myalgia, intense headache, arthralgia, vomiting, nausea and rashes. However, atypical presentations of dengue virus infection, including hepatitis, encephalopathy, cardiomyopathy, acute pancreatitis and acalculous cholecystitis, have been reported in recent years. Acalculous cholecystitis in a patient with DF is diagnosed when there is abdominal pain, vomiting and an optimistic Murphy's sign with a thickened gall bladder wall without gall-stones on ultrasound. Our research aimed to assess the incidence of acalculous cholecystitis in patients with Dengue and to evaluate its association with different lab parameters.

In our study, 49.6% of the patients diagnosed with Dengue fever had acalculous cholecystitis. Patients with DF have been diagnosed with acalculous cholecystitis in various other studies^{10,11}. Some studies have reported acalculous cholecystitis as a rare manifestation of dengue fever¹²⁻¹⁴. But an Indian study showed more than 38% of dengue patients to have cholecystitis¹⁵. The exact incidence was seen in Karachi¹⁶. A high percentage of acalculous cholecystitis was observed in dengue patients with capillary leak syndrome⁸.

Our research showed a higher percentage of cholecystitis because patients presenting to a tertiary care centre are more likely to have severe Dengue. Therefore, an ultrasound performed on these patients will show more frequent features of increased capillary permeability, like acalculous cholecystitis. Another reason could be that more secondary dengue infections are occurring now as DF has become endemic in Pakistan, and the same has been observed in other countries in the region.¹⁷ Secondary infections are expected to be more severe; thus, these patients have a higher incidence of acalculous cholecystitis.

The pathogenesis of acute acalculous cholecystitis in DF is still unclear. Bhatt P et al. showed that cholestasis, increased bile viscosity, and direct viral infection were the probable causes.¹⁸ However, the leading cause which induces the thickening of the gall bladder wall is increased vascular permeability, which causes plasma leakage¹⁹⁻²¹. Abnormal activity of T-cells and monocytes contributes to endothelial cell activation and leads to plasma leaking, which is mediated by complement activation and the production of different cytokines^{22,23}.

Acalculous cholecystitis in DF occurs in the critical phase of the disease and can predict the development of severe Dengue. DHF and DSS can develop in these patients unless appropriate management is instituted. These complications arise from increased capillary permeability with leakage of fluids during the critical phase of the disease; this is associated with

hemoconcentration. Our study has shown a significant association between hemoconcentration with acalculous cholecystitis. Other studies also confirm this^{8,24}. Our population is primarily anaemic; therefore, the hematocrit is low. We do not have a standard for normal hematocrit for our population. We retrospectively calculated hemoconcentration as a 20% increase in hematocrit compared to the convalescent sample²⁵. Thus, this investigation does not give us the advantage of predicting the development of complications in dengue fever. Some studies in India have defined definite hematocrit levels as predictors of hemoconcentration in pediatric populations in their specific regions^{26,27}. If we can develop similar values for our population, this would be a reliable and readily available prognosticator of severe DF.

Thrombocytopenia and leucopenia can also occur at the beginning of the critical phase of DF. Thrombocytopenia in itself is a feature of DF. In our study, this was also significantly associated with the development of cholecystitis. Thrombocytopenia in DF is thought to be due to the megakaryocytes' viral infection, which results in reduced platelet production, deranged platelet function, and increased destruction of platelets. Severe thrombocytopenia occurred in 24.6% of our patients and was observed in the two expiries because of the development of DHF followed by multi-system failure. The bleeding in DHF results from low platelet count, abnormality of platelet function and disseminated intravascular coagulation²⁵.

In other studies also, severe Dengue, associated with the development of capillary leak syndrome, was significantly associated with severe thrombocytopenia⁸.

Plasma leakage, hemoconcentration and abnormalities in homeostasis characterize severe Dengue. The mechanisms leading to severe illness are not well defined, but the immune response, the individual's genetic background, and the virus characteristics may all contribute to severe Dengue.

The development of thrombocytopenia and leucopenia precedes critical and severe Dengue. This was observed in our study, where a low platelet count of leucopenia, defined by a total leucocyte count of less than 4,000 per ml, was significantly associated with acalculous cholecystitis. Leucopenia has also been observed in other regional studies^{28,29}.

As the patient's condition worsens due to increased vascular permeability, they can develop hypotension and third space sequestration. Based on the extent of capillary permeability, this plasma leakage can be apparent as pleural effusion, ascites and acalculous cholecystitis.

While most symptomatic patients with DF recover after a short illness, a small proportion progress to more severe disease, typically manifesting as a vasculopathy characterized by plasma leakage and a

hemorrhagic diathesis. Plasma leakage may be profound, sometimes resulting in life-threatening dengue shock syndrome (DSS). Proactive management in the critical stage of DF may prevent the development of this condition. In our study, two mortalities occurred due to DHF and subsequent multiorgan failure. Both patients had third space fluid sequestration clinically apparent as ascites and presented with upper gastrointestinal bleeding and shock; the rest recovered with conservative management.

Although patients with acalculous cholecystitis had a significantly longer stay in the hospital, they did not require any surgical intervention. The study thus validates the conservative line of management for patients with acute acalculous cholecystitis in dengue fever.

This study emphasizes that improvements in clinical diagnosis of dengue and risk prediction for severe disease are urgently needed, especially in settings with a high case burden where appropriate allocation of limited resources is crucial to the outcome^{8,23,25}.

CONCLUSION

Acalculous cholecystitis is a common complication in Dengue fever and is associated with hemoconcentration, thrombocytopenia, leucopenia and hepatopathy; diagnosis of acalculous cholecystitis warrants prudent and proactive management to prevent Dengue Shock syndrome and Dengue Hemorrhagic fever. Acalculous cholecystitis caused by Dengue fever has a good prognosis with conservative management.

Dengue viral infection is a dangerous threat to global health. India faces a dengue crisis yearly, and death due to Dengue has risen alarmingly. Dengue is a highly unspecific illness with varied presentation and atypical manifestations. This study demonstrates and supports other studies indicating that early diagnosis and suspicion could improve outcomes. As Dengue is complex in presentation yet easier to treat, strict vigilance, symptomatic treatment, and adequate hydration are all required for recovery.

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AUTHOR CONTRIBUTIONS

Rasool FK: Literature search, data collection, statistical analysis, write up

Nageen A: Literature review, write up
Rasool AK: Literature search, data collection, statistical analysis, write up
Bashir F: Concept, statistics, review

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