SMJ Singapore Medical Journal

Acute acalculous cholecystitis in dengue fever: a case series

Yi Ting Lai[1], Shirin Kalimuddin[2], MBBS, MPH, Hannah Jia Hui Ng[3], MBBS, MRCS, Gerald Ci An Tay[4], MBBS, FRCSEd

[1]Yong Loo Lin School of Medicine, National University of Singapore, [2]Department of Infectious Diseases, Singapore General Hospital, [3]Department of Orthopaedic Surgery, Tan Tock Seng Hospital, [4]Department of Head and Neck Surgery, Singapore General Hospital, Singapore

Correspondence: Dr Gerald Tay Ci An, Senior Consultant, Department of Head and Neck Surgery, Singapore General Hospital, Outram Road, Singapore 169608. gerald.tay.c.a@singhealth.com.sg

Singapore Med J 2021, 1–12
https://doi.org/10.11622/smedj.2021168
Published ahead of print: 24 October 2021

INTRODUCTION

Dengue has rapidly emerged as a significant threat to public health since the 1950s, and is currently the fastest spreading mosquito-borne disease globally. The World Health Organization (WHO)[1] estimates that up to 50-100 million dengue infections occur annually, with over one-third of the world's population at risk.

Despite an aggressive vector-control program, dengue remains hyperendemic in Singapore, largely owing to the tropical climate and high population density. Major dengue epidemics have plagued the country over the years, with public health costs of each outbreak estimated to be over USD 40 million. In 2019 alone, close to 16,000 cases [2] of dengue were reported in Singapore – the highest number of annual cases in over five years.

The clinical spectrum of dengue ranges from a mild self-resolving illness with fever, rash and thrombocytopenia, to severe life-threatening disease characterised by vascular leakage, shock and haemorrhage. Treatment of dengue is primarily supportive, as no effective therapeutic currently exists. With rising disease burden however, the incidence of atypical manifestations of dengue fever have increased. Such atypical manifestations include acute acalculous cholecystitis (AAC).

Despite this, dengue-associated AAC has rarely been reported in the literature – only a few descriptive studies[3-5] and case reports were found in major literature over the past 15 years. Besides two individual cases reports from 2005[6] and 2006[7], data on the distribution, progression, and outcomes of patients presenting with dengue-associated AAC in Singapore is lacking. This case series aims to consolidate and review the clinical course and management of 12 cases identified in our institution from 2006-2015.

METHODS

Medical and imaging records of patients presenting to our institution between 2006 and 2015 with dengue fever and clinical suspicion of cholecystitis were reviewed retrospectively.

Dengue was confirmed in patients with a positive serum dengue IgM (Focus Diagnostics IgM Capture DxSelect), dengue PCR (in house assay based on pan-dengue primer sequences) or NS1 antigen (Bio-Rad Platelia Dengue NS1). The 12 cases of dengue-associated AAC were identified by positive dengue laboratory testing, presence of clinical signs consistent with acute cholecystitis according to Tokyo Guidelines for Acute Cholecystitis, radiological findings matching ultrasound or CT imaging criteria, in addition to the absence of cholelithiasis on imaging. Statistical analysis was performed using SPSS version 25.

The study was approved by the institutional ethics review committee (Ref No:2018/3204).

RESULTS

In our institution, there were 6931 admissions for dengue fever during the study period (2006-2015), of which 12 (0.17%) were diagnosed with dengue-associated AAC. 7 patients (58.3%) were male. The mean ± SD age was 49 ± 10.2 years. The mean ± SD length of hospital stay was 5 ± 1.9 days in patients who developed dengue-associated AAC while patients without AAC had a mean ± SD stay of 3.9 ± 2.3 days. A Mann-Whitney U test showed significant increase ($u=26703$, $p=0.03$) in length of hospital stay in patients who developed AAC (median =4.5) compared to those who did not (median = 4.0).

All 12 patients presented with right hypochondrial pain and fever on admission. Murphy's sign was positive in 5 patients (41.7%). 2 (16.7%) patients presented with bleeding manifestations (epistaxis, gum bleeding and petechiae). Pleural effusion was noted on chest radiographs of 8 patients (66.7%) and ascites was noted in 5 patients (41.7%), suggesting

presence of significant plasma leakage. Other presenting signs and symptoms are recorded in Table I. None of the patients had diabetes mellitus, ischemic heart disease, chronic kidney disease or underlying malignancy. Only 1 patient had hypertension.

7 (56.3%) patients had ultrasound imaging while 5 (41.6%) underwent CT imaging. Radiological findings are shown in Table II. Gallbladder wall thickening was noted in all 12 patients. The mean ± SD gallbladder wall thickness was 5.82 ± 0.31 mm.

The results of liver function tests and blood tests performed during hospital stay are detailed in Table III. In particular, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels were raised while albumin levels fell. Other abnormalities included thrombocytopenia, prolonged activated partial thromboplastin time (APTT) duration, as well as increased C-reactive protein (CRP) levels. Blood cultures were performed in 10 patients and none were found to be bacteraemic.

1 (8.3%) patient met the criteria for Dengue Haemorrhagic Fever (DHF) and 1 (8.3%) patient progressed to Dengue Shock Syndrome (DSS) under WHO 1997 dengue classification. The patient with DHF also had hypertension and received intravenous (IV) hydration while the patient with DSS received IV antibiotics and platelet transfusion.

4 (33.3%) patients were treated conservatively with IV hydration while 8 (66.7%) received empirical IV antibiotics. Transfusion of platelets and cryosupernatant plasma (CSP) was initiated respectively for 3 patients with severe thrombocytopenia, of which 1 had bleeding manifestations. None required surgery or invasive interventional procedures and all 12 patients were discharged uneventfully.

DISCUSSION

AAC is defined as an acute necroinflammatory disease of the gallbladder in the absence of cholelithiasis. Owen et al[8] summarised the various conditions that predispose to it, from

systemic sepsis to acute viral infection as commonly associated risk factors. Common but non-specific clinical findings include right hypochondrial pain, fever and abnormal liver tests.[9] This is consistent with the clinical presentation of our 12 patients. Severe complications including gangrene, perforation and empyema occur in 6-82% of people with AAC[10] and early intervention such as cholecystectomy and cystostomy are often proposed.[11] While AAC is associated with high mortality rates of up to 30%, this may be an epiphenomenon of the underlying severity of illness and is only rarely the primary cause of death.[12] Diagnostic ultrasound remains the imaging modality of choice with up to 100% specificity.[13] However, CT may aid in the diagnosis of AAC due to its high sensitivity and may be considered when other abdominal diseases are suspected.[14,15]

A few mechanisms have been hypothesised in the pathogenesis of AAC. Firstly, biliary stasis may result in altered bile composition, promoting gallbladder mucosal injury. Secondly, multiple arterial occlusions and microcirculatory disruption lead to gallbladder ischemia, which is central in the development of AAC. Lastly, release of vasoactive mediators such as pro-inflammatory eicosanoids stimulate inflammation and coagulation.[14] While the cause for development of AAC from dengue virus remains uncertain, it has been postulated that direct viral invasion of the gallbladder may be responsible for oedema and exudation.[4]

The first documentation of AAC as an atypical manifestation of dengue fever was in 2000.[16] Since then, there have been a few case reports and studies detailing the occurrence, with incidence rates varying from 6%[17] to 52%.[5] The stark difference in incidence rates may be due to different diagnostic criteria, especially since the clinical findings of AAC are often nonspecific.

The mean duration of hospital stay in our patients was 5 ± 1.9 days which is comparable to a mean duration of 5.1 ± 1.8 days reported previously by Navneet et al.[5] The latter prospective study also reported a significant increase in hospital stay for patients with dengue

fever and AAC. In our institution, a significantly longer hospital stay (u=26703, p=0.03) was likewise observed in patients admitted with dengue-associated AAC.

Laboratory findings commonly associated with dengue include neutropenia, lymphocytosis, increased concentrations of liver enzymes, and thrombocytopenia.[4] Mean AST (315.3 ± 208.9) (normal range: 12-42 U/L), ALT (178.8 ± 113.6) (normal range: 6-66 U/L) and ALP (119.2 ± 53.8) (normal range: 39-99 U/L) levels were raised and thrombocytopenia (60.8 ± 35.1) (normal range: 140-440 x 10^9/L) was noted in our patients. In addition, low mean albumin levels (32.25 ± 2.6) (normal range: 40-51 g/L) and high C-reactive protein levels (24.0 ±17.3) (normal range: 0-3 mg/dL) were also noted.

Sonographic findings such as thickened gallbladder wall, pleural effusion and ascites are also commonly cited.[3,4] In our patients, gallbladder wall thickening was the most common feature (100%), followed by positive sonographic murphy's sign (42.9%) and pericholecystic fluid collection (41.2%). Ascites and pleural effusion occurred in 41.7% and 66.7% of our patients respectively.

Previous studies have suggested that gallbladder wall thickening could be an indicator of ongoing plasma leakage,[18] and that a positive correlation exits between wall thickness and the development of DSS.[19] However, this was not observed in our study. Only 1 patient developed DSS and the gallbladder wall thickness was measured at 4.61 mm (normal range < 3 mm), which falls below the mean ± SD gallbladder wall thickness (5.82 ± 0.31 mm) in our study.

The usual treatment for AAC includes immediate cholecystostomy and/or cholecystectomy to prevent the feared complications of gangrene, empyema and perforation.[12] However, this does not appear to hold true for dengue-associated AAC. In our 12 cases, all cases recovered without surgical intervention. Treatment was conservative involving IV hydration, antibiotics and transfusion of blood products. However, a recently published

randomized controlled trial of dengue patients has shown no benefit in the use prophylactic platelet transfusions compared to supportive care alone in the absence of bleeding manifestations, and may instead be associated with increased adverse events.[20]

In dengue fever, AST and ALT levels typically rise in the first 8 days of illness but gradually decline and normalize by the third week.[21] Gallbladder wall thickening and ascites also resolves completely with recovery of acute dengue. It appears that surgical treatment is generally not indicated in dengue-associated AAC in the absence of complications such as gallbladder perforation. This is supported by the experience of others.[3,5,16-19] Surgical intervention in dengue-associated AAC may instead lead to unnecessary complications such as those from otherwise avoidable substantial blood transfusions, and significantly prolonged hospitalisation.[22]

This study was not without limitations. Our study was done retrospectively and information was dependent on the accuracy of the medical records.

While the imaging criteria has been well established, clinical signs of dengue-associated AAC are non-specific and diagnostic criteria vary amongst studies.[8,14] This may have led to the large differences in incidence rate amongst published studies. For our study, we referred to the Tokyo Guidelines for Acute Cholecystitis[23] and specific imaging criteria adapted from Huffman et al, 2001[5] for the definite diagnosis of dengue-associated AAC.

As the duration between onset of disease and admission to the hospital was variable, and the exact duration of individual symptoms were not always specified in the patients notes, the true values of varying clinical parameters may not have been determined precisely. For example, gallbladder wall thickness on imaging may be underestimated if sonography was done prior or after the plasma leakage phase, around the time of defervescence.[24]

In 2009, revised WHO guidelines for dengue severity classification[1] were published; Under the new classification guidelines, dengue fever is no longer classified as Dengue

Haemorrhagic Fever and Dengue Shock Syndrome. The new classification describes the severity of dengue fever based on presence of warning signs. However, the presence of such warning signs was not documented uniformly in the cases analysed and we were unable to classify our patients based on new guidelines. Nevertheless, classifying our patients based on the 1997 dengue fever guidelines[25] allowed meaningful comparisons with other studies that adopted the same dengue classification guidelines.

In conclusion, we found that dengue-associated AAC appears to be a distinct entity from other forms of AAC, and if uncomplicated, should be treated conservatively without the need for urgent surgical intervention.

REFERENCES

1. World Health Organization. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization, 2009.
2. Singapore NEA. Dengue Cases Singapore 2019. Available from: https://www.nea.gov.sg/dengue-zika/dengue/dengue-cases. Accessed October 15, 2021.
3. Wu KL, Changchien CS, Kuo CM, et al. Dengue fever with acute acalculous cholecystitis. Am J Trop Med Hyg 2003; 68:657-60.
4. Bhatty S, Shaikh NA, Fatima M, Sumbhuani AK. Acute acalculous cholecystitis in dengue fever. J Pak Med Assoc 2009; 59:519-21.
5. Sharma N, Mahi S, Bhalla A, et al. Dengue fever related acalculous cholecystitis in a North Indian tertiary care hospital. J Gastroenterol Hepatol 2006; 21:664-7.
6. Goh BK, Tan SG. Case of dengue virus infection presenting with acute acalculous cholecystitis. J Gastroenterol Hepatol 2006; 21:923-4.

7. Tan YM, Ong CC, Chung AY. Dengue Shock syndrome presenting as acute cholecystitis. Dig Dis Sci 2005; 50:874-5.

8. Owen CC, Jain R. Acute acalculous cholecystitis. Curr Treat Options Gastroenterol 2005; 8:99-104.

9. Laurila J, Laurila PA, Saarnio J, et al. Organ system dysfunction following open cholecystectomy for acute acalculous cholecystitis in critically ill patients. Acta Anaesthesiol Scand 2006; 50:173-9.

10. Kalliafas S, Ziegler DW, Flancbaum L, Choban PS. Acute acalculous cholecystitis: incidence, risk factors, diagnosis, and outcome. Am Surg 1998; 64:471-5.

11. Glenn F, Becker CG. Acute acalculous cholecystitis. An increasing entity. Ann Surg 1982; 195:131-6.

12. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. Clin Gastroenterol Hepatol 2010; 8:15-22.

13. Pelinka LE, Schmidhammer R, Hamid L, Mauritz W, Redl H. Acute acalculous cholecystitis after trauma: a prospective study. J Trauma 2003; 55:323-9.

14. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin North Am 2010; 39:343-57, x.

15. Mirvis SE, Vainright JR, Nelson AW, et al. The diagnosis of acute acalculous cholecystitis: a comparison of sonography, scintigraphy, and CT. AJR Am J Roentgenol 1986; 147:1171-5.

16. Sood A, Midha V, Sood N, Kaushal V. Acalculous cholecystitis as an atypical presentation of dengue fever. Am J Gastroenterol 2000; 95:3316-7.

17. Nimmagadda SS, Mahabala C, Boloor A, Raghuram PM, Nayak UA. Atypical manifestations of dengue fever (DF) - where do we stand today? J Clin Diagn Res 2014; 8:71-3.

18. Nainggolan L, Wiguna C, Hasan I, Dewiasty E. Gallbladder wall thickening for early detection of plasma leakage in dengue infected adult patients. Acta Med Indones 2018; 50:193-9.

19. Setiawan MW, Samsi TK, Pool TN, Sugianto D, Wulur H. Gallbladder wall thickening in dengue hemorrhagic fever: an ultrasonographic study. J Clin Ultrasound 1995; 23:357-62.

20. Lye DC, Archuleta S, Syed-Omar SF, et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial. Lancet 2017; 389:1611-8.

21. Wang LY, Chang WY, Lu SN, Chen TP. Sequential changes of serum transaminase and abdominal sonography in patients with suspected dengue fever. Gaoxiong Yi Xue Ke Xue Za Zhi 1990; 6:483-9.

22. Khor BS, Liu JW, Lee IK, Yang KD. Dengue hemorrhagic fever patients with acute abdomen: clinical experience of 14 cases. Am J Trop Med Hyg 2006; 74:901-4.

23. Takada T. Tokyo Guidelines 2018: updated Tokyo Guidelines for the management of acute cholangitis/acute cholecystitis. J Hepatobiliary Pancreat Sci 2018; 25:1-2.

24. Srikiatkhachorn A. Plasma leakage in dengue haemorrhagic fever. Thromb Haemost 2009; 102:1042-9.

25. World Health Organization. Dengue Haemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. 2nd ed. Geneva: World Health Organization, 1997.

Table I: Associated signs/symptoms and complications

Associated signs/symptoms	n/N (%)
Fever	12/12 (100%)
Abdominal Pain	12/12 (100%)
Right Hypochondrial Pain	12/12 (100%)
Pleural Effusion	8/12 (66.7%)
Myalgia	6/12 (50%)
Ascites	5/12 (41.7%)
Murphy's Sign	5/12 (41.7%)
Rash	2/12 (28.6%)
Arthralgia	3/12 (25%)
Epistaxis	1/12 (0.83%)
Gum Bleeding	1/12 (0.83%)
Haematemesis	0/12 (0%)
Melena	0/12 (0%)

Table II: Ultrasound/ computed tomography imaging findings

Imaging criteria	Modality	Type	n/N (%)
Gallbladder Wall Thickening	US[1]/CT[2]	Major	12/12 (100%)
Pericholecystic Fluid Collection	US/CT	Major	5/12 (41.2%)
Echogenic Bile (sludge)	US/CT	Minor	0/12 (0%)
Distended Gallbladder	US/CT	Minor	0/12 (0%)
Positive Sonographic Murphy's sign	US	Major	3/7 (42.9%)
Striated Gallbladder	US	Major	2/7 (28.6%)
Pericholecystic Fat Stranding	CT	Major	2/5 (40%)

[1] US: Ultrasonography

[2] CT: Computed Tomography

Table III: Results of blood and liver function tests

Blood Tests Results	**Mean ± SD**[1]		
	Overall	DHF[2]	DSS[3]
Haemoglobin level (g/dL) (F: 12-16)	14.0 ± 1.4		
Haemoglobin level (g/dL) (M:14-18)	16.0 ± 2.0	14.5	**18.8**
Haematocrit (%) (F: 36-46)	41.3 ± 4.2		
Haematocrit (%) (M: 38-52)	45.7 ± 5.8	40.6	**52.7**
White blood cell count (x10^9/L) (4-10)	5.2 ± 3.5	**2.05**	**2.69**
Platelet count (x10^9/L) (140-440)	**60.8 ± 35.1**	**53**	**12**
Prothrombin time (s) (9.9-11.4)	10.5 ± 0.8	**11.7**	11.3
Activated Partial Thromboplastin Time (s) (25.7-32.9)	**46.7 ± 10.8**	**50.2**	**66.3**
C-Reactive Protein (mg/dL) (0-3.00)	**24.0 ±17.3**	**4.6**	**54.3**
Liver Function Tests Results			
Aspartate aminotransferase (U/L) (12-42)	**315.3 ± 208.9**	**285**	**271**
Alanine aminotransferase (U/L) (6-66)	**178.8 ± 113.6**	**232**	**91**
Alkaline Phosphatase (U/L) (39-99)	**119.2 ± 53.8**	**87**	**160**
Total Bilirubin (umol/L) (7-32)	19.5 ± 11.3	16	17
Albumin (g/L) (40-51)	**32.3 ± 2.6**	**33**	**28**
Serum Amylase (U/L) (38-149)	70.3 ± 38.7	77	NA

[1] SD: Standard deviation

[2] DHF: Patient with Dengue Haemorrhagic Fever

[3]DSS: Patient with Dengue Shock Syndrome

Normal range values in brackets

APPENDIX

Supplementary material

Imaging criteria for acute acalculous cholecystitis (adapted from Huffman *et al*, 2001)[12]

Modality	Criteria		Diagnosis
US[1]	**Major**	3.5- to 4-mm (or more) thick wall (if at least 5-cm distended longitudinally with no ascites or hypoalbuminemia) Pericholecystic fluid (halo)/subserosal edema Intramural gas Sloughed mucosal membrane	2 major or 1 major and 2 minor
	Minor	Echogenic bile (sludge) Hydrops distension greater than 8-cm longitudinally or 5-cm transversely (with clear fluid)	
CT[2]	**Major**	3- to 4-mm wall thickness Pericholecystic fluid Subserosal edema Intramural gas Sloughed mucosa	
	Minor	Hyperdense bile (sludge) Subjective distension (hydrops)	

[1] US: Ultrasonography

[2] CT: Computed Tomography