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Dengue fever may mislead the surgeons when it presents as an acute abdomen

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ABSTRACT

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Objective: To review the management experience of a consecutive series of patients presenting as acute surgical abdomen whom were ultimately diagnosed to have DF (Dengue fever)/DHF (Dengue hemorrhagic fever).

Methods: Clinical data of all cases of apparent acute abdomen (AA) which were later confirmed as having DF/DHF reviewed by two surgical units from December 2012 to December 2013 were analyzed. Initially confirmed patients with DF/DHF who developed abdominal symptoms were not considered.

Results: Out of the seventeen cases (7 males, age range 10–71 years) presented with fever and AA; appendicitis, cholecystitis, pancreatitis and non-specific peritonitis were suspected initially in 8, 5, 1 and 3 cases, respectively. Neutropenia or thrombocytopenia signifying DF/DHF occurred only in 11 patients at first evaluation thus six remained as surgical candidates beyond 24 h. One patient underwent appendicectomy with a prolonged hospital stay. DF was confirmed by serology in all patients, latest by fourth day of admission. One required blood product transfusion, 4 needed critical care treatment and there was 1 death.

Conclusions: DF/DHF misleads the clinicians when it presents as AA. Initial hematological and ultrasonographic findings may be equivocal creating a diagnostic and management dilemma. Vigilant clinical suspicion and early dengue serological assessment is advisable in equivocal cases of AAs with fever in dengue endemic areas, to confirm/exclude the infection in order to avoid unnecessary surgical morbidity in the presence of DF.

1. Introduction

Dengue fever (DF) is the commonest vector borne viral infection worldwide. The World Health Organization (WHO) considers dengue to be the most rapidly spreading arthropodborne viral infection of the globe. There would be around 50 million reported cases per year around the world disseminated over 100 countries, mainly in tropics. This has resulted in a significant health, economic and a social burden to the affected countries [1,2]. Worldwide there would be at least 24000 deaths attributed to dengue annually [3]. Dengue fever has been endemic in most parts of Sri Lanka and there have been several outbreaks during the last decade. There were 29777 reported cases of dengue in 2015 in Sri Lanka and the count has

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exceeded 31500 during the first seven months of 2016, with western province accounting for more than 45% of cases [4]. Clinical spectrum of dengue may range from undifferentiated self-limiting febrile illness to dengue haemorrhagic fever (DHF) leading to dengue shock syndrome (DSS) [1-3]. Although abdominal pain or severe gastrointestinal involvement is a recognized feature during the critical phase of DHF (from the 3rd to 7th day from the onset of fever) [1,3,5], dengue fever presenting as a surgical emergency with acute abdomen is rare. There are a limited number of case series and sporadic case reports of patients with DF/DHF presenting as acute abdomen to surgical emergency units, misleading the clinicians resulting in complicated outcomes [6-17]. DHF/DSS with or without coagulopathy creates significant derangements to body's homeostasis with microvascular changes resulting in high morbidity and even mortality. In such background, misdiag nosing DHF/DSS as a surgical acute abdomen may potentially result in significant negative outcomes. Therefore early identification of patients with DF/DHF presenting as acute abdominal emergencies to the surgeons is of great importance to prevent unnecessary surgical interventions which may result in added morbidity, costs and even mortality. In this retrospective study we describe the management outcomes of a consecutive series of patients with an ultimate diagnosis of DF/DHF, who presented as an acute abdomen to two surgical units in two teaching hospitals in western province of Sri Lanka.

2. Material and methods

After observing a surge of dengue cases presenting as acute abdomens to the surgical units, clinical and demographic data of all such cases of apparent acute abdomens which were later confirmed as having DF/DHF initially reviewed by two surgical units at National Hospital of Sri Lanka and Colombo South Teaching Hospital from December 2012 to December 2013 were evaluated. Follow up details were recorded at subsequent clinic reviews or by a telephone review after three months. For this review a case of 'acute abdomen' was defined as a patient who presents with rapid onset abdominal pain and fever as the main complaint with evidence of peritonism on examination. Presumptive diagnosis of acute abdomen was evaluated at two stages; first at the level of the referring general practitioner, the hospital admitting medical officer or the attending physician prior to surgical review and secondly after the assessment of a senior member of the surgical team. Cases initially diagnosed or suspected as DF/ DHF who developed abdominal symptoms were not considered for the evaluation. Dengue infection was confirmed by identification of Dengue Ig M antibody or Dengue NS antigen in the serum during the admission. DHF and dengue shock syndrome were categorized according to WHO definitions [18]. Initial management was carried out according to the presumptive surgical diagnosis and subsequently according to Sri Lankan dengue guidelines once the DF/DHF were confirmed [5].

Ethical approval was obtained from the ethical review committee of the National Hospital of Sri Lanka.

3. Results

A total of 3309 cases of DF/DHF were reported in the two institutions during the study period. There were 17 cases (7 males, Age range 10-71 years), with a presumptive diagnosis of an acute abdomen fulfilling the inclusion criteria of the study. Twelve patients were initially admitted to the surgical unit as evaluated by the referring general practitioner or the hospital accident and emergency admitting officer. Other 5 cases were admissions to medical units due to abdominal pain and fever referred to the surgeons by the physicians after their initial assessment with suspicion of acute appendicitis (2 cases), acute cholecystitis (2 cases) and acute pancreatitis (1 case). In addition to abdominal pain and fever seen in all cases in the series, the other clinical features that were elicited at the time of the assessment of the surgical team are summarized as follows: nausea/vomiting 11 cases (65%), watery diarrhea 3 (18%), myalgia/arthralgia 2 (12%), headache 2 (12%), skin rashes 2 (12%), haemorrhagic manifestations 1 (6%), shock 1 (6%), rebound tenderness of right ileac fossa 7 (41%), Murphy's sign 5 (29%), Rovsing's sign 4 (24%) and diffuse peritonism 4 (24%).

Out of the 17 cases, appendicitis and cholecystitis were suspected initially in 8 and 5 cases, respectively prior to the evaluation of the surgeons. One patient seemed to have pancreatitis and three were suspected to have nonspecific peritonitis. Four out of five cases of presumptive cholecystitis had a previous history of cholelithiasis and the suspected case of acute pancreatitis had past episodes of alcohol related pancreatitis. Following the clinical evaluation by the surgeons prior to assessing hematology and serum biochemistry, DF/DHF was suspected as the primary working diagnosis in three out of seventeen cases of presumptive acute abdomen. Leucopenia less than 5000/mm³ was seen in 7 cases and thrombocytopenia less than 150000/mm³ was seen in 9 patients on first evaluation. A summary of deranged initial hematological investigation results at the admission are given in Table 1.

Possibility of DF/DHF was suspected in 11 cases within the first 24 h of admission, following the hematological investigation review. Thus 6 patients remained as 'surgical candidates with acute abdomens' after clinical assessments by surgeons and basic hematological investigations. Two cases each were considered as having acute appendicitis and acute cholecystitis and one case each was considered as having acute pancreatitis and nonspecific peritonitis at this stage. The first patient in the series with a tentative clinical diagnosis of acute appendicitis (aided by an initial total white cell count of 7 200/mm³ with 79% neutrophil count and normal platelet count of 195000/mm³) underwent appendicectomy, with operative findings compatible with appendicitis [17]. He had worsening peritonism after 24 h and had a re-exploration at 36 h from first surgery with a suspected bowel injury or a slipped ligature. Although there was neutropenia (3400/mm³) and marginal thrombocytopenia (147000/mm³) prior to the second exploration, possibility of dengue fever never crossed the minds of the surgeons until the negative re-exploration. He developed dengue shock syndrome and had further thrombocytopenia up to 46000/mm³ without bleeding manifestations. He required level two care but did not need blood product transfusion. There was a second young female patient (with an initial total white cell count of 7900/mm³ with 69% neutrophil count, platelet count of 174000/mm³ and CRP of 14 mg/L) who was planned for a diagnostic laparoscopy to proceed to appendicectomy following day with a presumptive diagnosis of acute appendicitis after an evening admission. She was confirmed to have DSS by next morning due to shock and mucosal bleeding. As both surgical units do not consider emergency laparoscopic cholecystectomy for 'hot gallbladders', none of the cases thought as having acute cholecystitis were planned for emergency surgery.

Table 1

Summary of deranged initial hematological investigation results at the admission.

Deranged investigation	n/N (%)
Thrombocytopenia (<150000/mm ³)	9/17 (53)
Leucopenia (<5000/mm ³)	7/17 (41)
Lymphocytosis (>4000/mm ³)	12/17 (71)
Elevated AST (>40 U/L)	5/10 (50)
Elevated ALT (>40 U/L)	3/10 (30)
Elevated amylase (>125 U/L)	1/6 (17)
Prolonged INR (>1.4)	1/3 (33)
Elevated CRP (>12 mg/L)	4/14 (29)

(n - Number of patients, N - Number of patients with availability of data, AST - Aspartate transaminase, ALT - Alanine transaminase, INR - International normalized ratio, CRP - C-Reactive Protein).

Dengue infection was confirmed by serology in all seventeen patients, latest by fourth day of admission (Mean 1.8 days, Range 1-4). Out of them, sixteen had evidence of plasma leakage to confirm DHF. Four cases progressed to DSS and needed critical care support. All patients were evaluated by ultrasonography of the abdomen either to clarify the presumptive surgical diagnosis or to assess evidence of plasma leakage after suspecting DHF. Twelve patients had evidence of free fluid in the abdomen confirming plasma extravasation. Out of them, ten patients including all five suspected cases of cholecystitis had edema around the gallbladder or traces of free fluid in the Morrison's pouch. Three cases had traces of free fluid in right ileac fossa with no other evidence appendicitis. There was one death in the series. A 71 year old patient with a background history of ischemic heart diseases and decompensated liver disease, who remained as a case of non-specific peritonitis after first 24 h, succumbed due to DSS and bleeding diathesis five days after the admission. DHF was diagnosed on the second day of admission and abdominal ultrasonography showed gross ascites. He was the only patient in the series who required blood product transfusion due to melena and hematochezia. All sixteen surviving patients were well at three months of hospital discharge. Four patients who had history of gallstones underwent uncomplicated laparoscopic cholecystectomies within next twelve months.

4. Discussion

Although development of abdominal pain and presence of abdominal tenderness are known features in DHF, disease presenting as an acute abdomen is rare. There are limited number of case series and isolated case reports proving this clinical entity [6-17]. Out of them, some patients have been subjected to invasive surgical procedures leading to added morbidity and prolonged hospital stay [6-8,16,17]. DHF with or without shock or coagulopathy creates significant derangements to body's homeostasis, thus misdiagnosing dengue as a surgical acute abdomen may result in negative outcomes in several ways. Firstly, the time window of the early critical phase of DHF which can be used for targeted fluid management would be missed and secondly, the use of non-steroidal anti-inflammatory drugs and intramuscular analgesics for a perceived acute abdomen may aggravate bleeding manifestations of DHF. Thirdly, subjecting a patient to a surgical intervention for a suspected acute abdomen during the critical phase of DHF may potentially lead to disastrous outcomes. Therefore early identification of such patients is important in order to avoid negative end results.

In a series of 328 cases of DHF, Khor *et al.* presented 14 patients (4.3%) who developed acute abdomens and 163 (49.7%) to have develop non-specific abdominal pain without clinical signs [6]. Shamim *et al.* reported 43 (12.0%) acute abdomens and 276 (77.3%) cases of non-specific abdominal pain without clinical signs in his series of 357 patients with DHF [8]. In addition, Weerakoon *et al.* mentioned of 14/337 patients with DHF to have acute abdominal pain severe enough to keep only on intravenous fluids while being treated in medical units [19]. Therefore it is understandable that a significant proportion of patients (50–75%) with DHF would develop abdominal pain and about 5–10% of cases to proceed to a level that would mimic an acute abdomen with peritonism. All such patients belonging to the latter category are at risk of being considered as pure surgical candidates.

Verdeal *et al.* further emphasized this by stating acute abdomen (including gastroenteritis, appendicitis, cholecystitis, pancreatitis and viscus perforation) as a differential diagnosis for severe dengue infection [3].

The current series highlights the fact that misinterpretation of the acute abdominal signs and symptoms of DF/DHF may happen at different levels of medical triage. Due to the variable nature of presentation, seventeen dengue cases were considered as surgical 'acute abdomens' by primary care physicians and out of them 5 cases have been even reviewed by the hospital general medical team. Only 3 cases were suspected as DF/DHF after the clinical evaluation by the surgeons, further proving the equivocal nature of the clinical presentation. Presence of a previous surgical disease like gallstones or pancreatitis would have easily deceived the clinicians by making them biased at decision making. A neutropenia, lymphocytosis or thrombocytopenia would be generally expected in DF/DHF, but these changes may not be apparent in all early samples. Initial hematological findings may be equivocal worsening the diagnostic dilemma. In our series hematological changes of DF/DHF were apparent only in 11 cases during first 24 h and 6 patients remained as pure surgical candidates with suspicion of acute appendicitis, acute cholecystitis, acute pancreatitis and nonspecific peritonitis.

Greatest risk associated with the misdiagnosis of DF/DHF as an acute abdomen is subjecting of them to surgical intervention. Consideration for surgery would not just be 'wrong treatment' but would open up a pathway for complications due to multiple organ system instability and coagulopathy seen in DHF patients. According to common surgical belief acute appendicitis requires appendicectomy to prevent local and systemic complications and surgeons attempt to complete surgery without delay as an emergency [20-22]. Actions taken upon such belief led to the only complicated surgery in the current series [17]. Khor et al. reported one patient and Shamim et al. reported five cases undergoing appendicectomy in their respective series, later necessitating blood product transfusion [6,8]. Premaratna et al. has reported a series of twelve patients with DHF presenting as acute appendicitis and one patient in his series underwent appendicectomy with a prolonged hospital stay [7]. To complicate the matters further the patient who underwent appendicectomy in the current series had histological evidence of acute appendicitis with transmural neutrophil infiltration in the background of DHF [7]. Senanayake and Samarasinghe have recently described a case of appendicitis with mass formation in the background of serologically proven dengue infection [23]. Such presentations could easily mislead the clinicians.

Acute calculous cholecystitis may be initially managed conservatively with supportive care with subsequent cholecystectomy after several weeks or with an emergency laparoscopic cholecystectomy within the first 72 h of onset of symptoms [24]. As our units consider the earlier pathway, emergency surgery was not considered in all suspected cases of cholecystitis. Similarly, acute acalculous cholecystitis needs to be managed with supportive care, antibiotics and emergent laparoscopic cholecystectomy as it is more prone for gangrenous perforation than the calculous counterpart. However as this entity is seen mainly in critically ill or immune compromised patients, most cases may not be suitable candidates for emergency surgery thus requiring percutaneous drainage [24]. Khor et al., Shamim et al. and Wu et al. in combination considered six cholecystectomies and two percutaneous gallbladder drainages in their series of DHF suspecting gangrenous cholecystitis [6,8,16]. Although all those cases survived, all of them required blood product transfusion

Table 2

Comparison between the current series and similar case series where patients with DHF were subjected to interventions due to presumptive diagnosis of acute abdomen.

Author/(Year)/ Country/[Reference]	Study duration (Months)	n/N	Initial presumptive diagnosis	Interventions [Complication/s]
[#] Wu <i>et al.</i> (2003) Taiwan [16]	10	10/131	Acute cholecystitis 10	Cholecystectomy 2; Percutaneous drainage 1; [Blood product transfusion 3; Prolonged stay 3];
Khor <i>et al.</i> (2006) Taiwan [6]	7	14/328	Acute cholecystitis 10 Acute appendicitis 1 Non-specific peritonitis 3	Appendicectomy 1; Cholecystectomy 1; Percutaneous drainage 1; [Blood product transfusion 3; Prolonged stay 3]
[#] Premaratne <i>et al.</i> (2007) Sri Lanka [7]	9	12/NA	Acute appendicitis 12	Appendicectomy 1; [Prolonged stay 1];
Shamim <i>et al.</i> (2010) Pakistan [8]	43	43/357	Acute cholecystitis 26 Acute appendicitis 7 Non-specific peritonitis 7 Acute pancreatitis 3	Appendicectomy 5; Cholecystectomy 3; [Bleeding manifestations 8; Blood product transfusion 8; Prolonged stay 8]
Present study (2016) Sri Lanka	12	17/3309	Acute cholecystitis 5 Acute appendicitis 8 Non-specific peritonitis 3 Acute pancreatitis 1	Appendicectomy 1; [Prolonged stay 1]

Notes: [#]These studies only considered a specified disease diagnosis than broadly evaluating acute abdomens in the presence of DF/DHF, NA – Not available; *n*/*N*: Cases of DF presenting as acute abdomen/Total number cases with DHF.

and had a prolonged hospital stay. As plasma leakage with pericholecystic edema is a well-recognized feature in DHF the surgeons could be easily mislead by the equivocal clinical picture.

As operative surgery is not considered as the main stay of treatment for acute pancreatitis within first (24-72) h, DHF cases that are perceived as acute pancreatitis are less likely to be intervened by the surgeons. However as acute pancreatitis is treated with aggressive fluid resuscitation to minimize complications, such patients with DHF presumed as having acute pancreatitis are at theoretical risk of developing fluid overload during the recovery phase of DHF. DHF cases that are presumed as nonspecific peritonitis are unlikely to be surgically intervened without further imaging modalities and the time taken for such investigations may provide opportunity for the clinicians to rectify the mistaken diagnosis. Although all reported cases that had surgical interventions in the midst of DHF survived, most had substantial amounts of blood product transfusions and prolonged hospital stays [6-8,16]. Table 2 summarizes a comparison between the current series and the previous case series, where patients were subject to surgical procedures due to presumptive diagnosis of acute abdomen in the background of DF/DHF.

Exact mechanism of acute abdomen and peritonism seen in DHF is unclear. Wu et al. postulated cholestasis, endotoxemia, microangiopathy, ischemia and reperfusion injury as possible pathogenic mechanisms for acute acalculous cholecystitis in DHF [16]. Although Shamim et al. reports the presence of gangrenous patches in one out of three cholecystectomies in his series, there is no availability of microscopic evidence cholecystitis in any of the cases undergoing cholecystectomy in the background of DHF [8]. In his series all five patients who underwent appendicectomy for suspicion of perforated appendix, none had perforations [8]. Wu et al. found lymphocytic infiltration of the gallbladder wall in both cases that had cholecystectomy in the background of DHF [16]. Other than for the first patient in the current series who had microscopic evidence of appendicitis with transmural neutrophil aggregation, none of the other cases of DHF who underwent appendicectomy had shown histological evidence of

appendicitis. This evidence confirms that the clinicians have been deceived by the ambiguous clinical picture created by DHF.

Current series highlights the dilemma created by equivocal clinical picture of DHF when it presents as an acute abdomen. Despite being aware that abdomen related clinical features may occur in a reasonable percentage of patients with DHF, clinicians of various levels including primary care practitioners, physicians and surgeons were misled by the cases of DF/DHF that presented as acute abdomens. That led to potentially avoidable surgeries, blood product transfusions and prolonged hospital stays which could have been avoided. Therefore it is important that all medical practitioners in dengue endemic areas to be vigilant on this matter and understand the ambiguous nature of DHF leading to peritonism. Especially the surgeons have to be cautious on managing acute abdomens with fever in dengue affected areas as subjecting such a case for surgery can lead to disastrous outcomes. However, it should also be understood that there could also be possible negative impacts of delaying the surgical interventions on a 'true' peritonitic patient in the suspicion of DHF. Therefore, when dealing with an equivocal case with acute abdomen and fever in a dengue endemic area, it is of paramount importance that the surgeons suspect DHF early as a differential diagnosis and confirms or excludes the infection using serology before subjecting the patient to surgical intervention.

Conflict of interest statement

We declare that we have no conflicts of interest.

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