СЛУЧАИ ИЗ ПРАКТИКИ

HAEMORRHAGIC DENGUE FEVER: A CASE REPORT FROM BRAZIL

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Dengue fever (DF) is a common cause of arboviral infections in South America, belonging to the genus Flavivirus. Only in Fortaleza, the 5th most populated city in Brazil, in the year of 2011 over 110 cases of dengue fever by day were being registered [3]. DF is only rarely considered as a cause of acute liver failure [4], while this particular case involves three different systems, being the reason why it called our attention. 50 year old, male, conscious, presents to São José Hospital of Infectious Diseases with classic dengue fever symptoms, being the day of his admission the 9th since the first symptoms erupted. Other causes for acute hepatic failure like acute viral hepatitis, leptospirosis, malaria, Reyes syndrome were ruled out, had the patient already been tested for dengue IgM in a local hospital. Complained of a pain in his abdomen, simple thorax radiography showed an enlarged cardiac area. His ECG reinforced the cardiac enzymes' results, showing a clear alteration in ventricular repolarization. Patient progressed with shock, cardiac insufficiency and ischemic hepatitis. With treatment for the multiple conditions he made a significant clinical and biochemical improvement. He was discharged after 33 days of hospital stay.

Key words: Dengue fever, Flavivirus, infectious diseases, viral hemorrhagic fevers, tropical diseases, brazil, case study, Aedes aegypti.

A dengue case is suspect on each patient presenting fever, with a maximum duration of seven days, accompanied by at least two signs or symptoms such as headache, retro-orbital pain, myalgia, arthralgia, prostration or rash, with or without the presence of bleeding or hemorrhage, with positive epidemiological history, having been in the last 15 days in a dengue transmission area that has the presence of *Aedes aegypti*. As there is no specific treatment for dengue fever, good fluid intake (water, juices, soups, etc.), rest and symptomatic treatment as per the advice of a family physician is the only treatment.

There is no vaccine available for dengue so far. The appropriate management of patients depends on early recognition of alarm signals, the continuous monitoring and fluid reposition. With this, it becomes necessary the review the clinical history, physical examination accompanied by each reassessment of the patient, proper registration (clinical records) and notification of Healthcare authorities. We describe our former patient presenting blood results and other clinical examinations and the course of treatment taken.

Patient admission — Physical examination and blood work. 50 year old, male, conscious has been admitted to the ER of São José Hospital of Infectious Diseases with a history of fever and headache nine days prior to his admission. Relates that has been getting worse for three days now, worsening which is associated with abdominal pain and respiratory discomfort (Kussmal breathing) and worsening adynamia. Patient on his physical exam shows BP hypotension.

Patient then denies any alteration of his intestinal functions, bleedings, and altered sensorium. Diarrhea, present in 48% of cases [5], usually is not bulky, with a frequency of three to four bowel movements per day, which facilitates the differential diagnosis with other causes of gastroenteritis. The family reports that the patient's urine was very concentrated (but no hematuria) and that the patient complains about a pain in the superior part his abdomen, which had started three days prior to that. The Tourniquet test (TT) — a capillary fragility test — should be used in clinical practice as an element screening for suspected dengue. A positive TT is a frequent manifestation in dengue fever, especially in severe forms (Dengue Hemorrhagic Fever) and despite of not being specific, serves as a warning for the risk of progression to severe forms. A blood pressure cuff is applied and inflated to the midpoint between the systolic and diastolic blood pressures for five minutes. The test is positive if there are more than 10 to 20 petechiae per a circle of 2.5 cm (1 inch) of diameter. In DHF the test usually gives a definite positive result with 20 petechiae or more. Tourniquet test was not performed, as we had already the dengue IgM results. Also because IgM testing is a better venue for dengue diagnosis at his later stage of the disease, as known, dengue fever usually lasts a week and secondly, for being a more specific test. He was admitted to the ER with arising complications of the latter.

Laboratory results and other examinations. According to his blood work [table 1] he shows leukocytosis (22.310/mm^3); elevated transaminases, such as: AST 1.254 IU/L and GPT 1818 IU/L; urea 92 mg/dL; creatinine levels of 1,2 mg/dL; glucose 231 mg/dL; LDH 2.333 IU/L; elevated lactate of 100,5 mg/dL; CK total 3.954 IU/L; CPK-MB 161,6 IU/L.

Table 1

Admission exams

	Patient's values	Reference values
↑ Leukocytes	22.310/mmi	4.100—10.900/mmi
↑ AST	1.254 IU/L	5—35 IU/L
↑ GPT	1.818 IU/L	
Creatinine	1,2 mg/dL	0,5—1,4 mg/dL
CK	3.954 IU/L	60—400 IU/L
CPK-MB	161,6 IU/L	
↑ Glucose	231 mg/dL	65—110 mg/dL

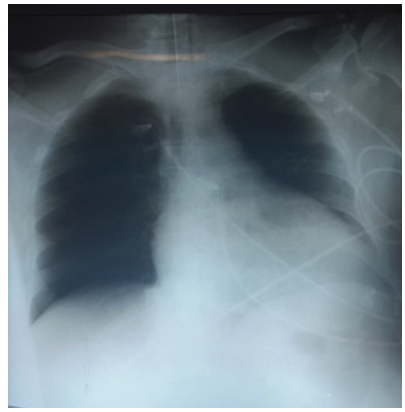
On his blood count, we got decreasing Hematocrit values, 49,9 (day 3), 41,5 (day 11), 37,2 (day 15), 21,5 (day 19). As we can see from the above given, he presented

a high value on day 3, which then decreased thanks to the fluid intake during his hospital stay. High hematocrit due to fluid loss is common to dengue fever. In hemorrhagic dengue fever, there is enlargement of prothrombin time and activated partial thromboplastin, decreased fibrinogen and reduction of clotting factors II, V, VII, X and XII, as shown in his blood work (day 10): Prothrombin time — 12,9 seconds. Prothrombin activity — 102% (reference 70—100%). And platelet count remained in its normal ranges (reference 150,000—400,000): 203.000 (day 3), 328.000 (day 6), 382.000 (day 9), 208.000 (day 16), 186.000 (day 20) — even though it is common to be low with dengue fever.

Taken all the above in consideration, our patient belongs to the higher group risk (*Red Group D*) for dengue patients. This classification is promoted by the Brazilian Ministry of Healthcare to reduce the waiting line in the ER room and to give care to the most endangered patients. Classification is often used during epidemics. That is: 1) *Blue*: Group A — care according to the arrival time; 2) *Green*: Group B — non-urgent priority; 3) *Yellow*: Group C — urgent care ASAP; 4) *Red*: Group D — emergency patient in need of immediate care.

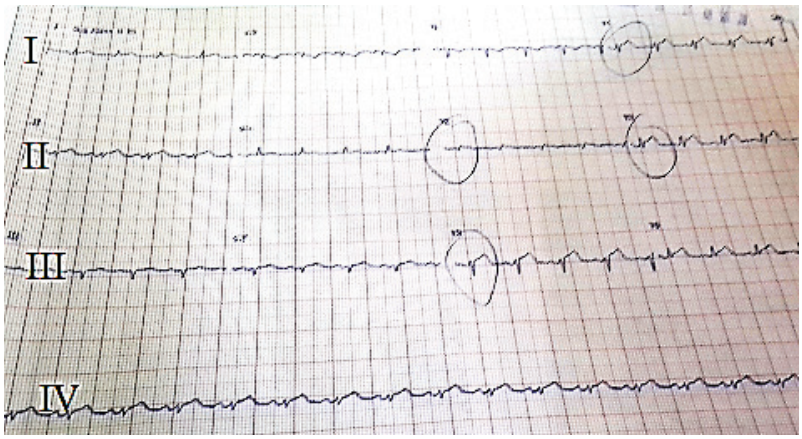
Further development and clinical complications. Patient presented exanthema, which usually is present in 50% of the dengue cases. Between the third and seventh day of illness onset it is common to occur intense and continuous abdominal pain, discomfort breathing (in this case, Kussmal's), tender hepatomegaly, the latter which was confirmed with an ultrasound. Other causes for acute hepatic failure like acute viral hepatitis, leptospirosis, malaria, Reyes syndrome were ruled out, as had the patient already been tested for dengue IgM in a previous local medical facility. All of these alarm signs should alert doctors to a possible upcoming shock:: a) severe abdominal pain and continuous; b) persistent vomiting; c) postural hypotension and / or syncope; d) tender hepatomegaly; e) mucosa bleeding or major bleeding (hematemesis and / or melena); f) somnolence and / or irritability; g) decreased urine output; h) a sudden drop in body temperature, or hypothermia; i) sudden increase in hematocrit; j) abrupt fall in platelets; l) respiratory distress.

Even though alarm signs of the clinical condition worsen usually in *remission fever* (between the 3rd and 6th day of the disease), our patient continued to present them and to worsen his general state as late as during the second week of the fever. Other examinations, including a simple thorax radiography, show an enlarged cardiac area [Picture 1].



Pic. 1. Cardiomegaly

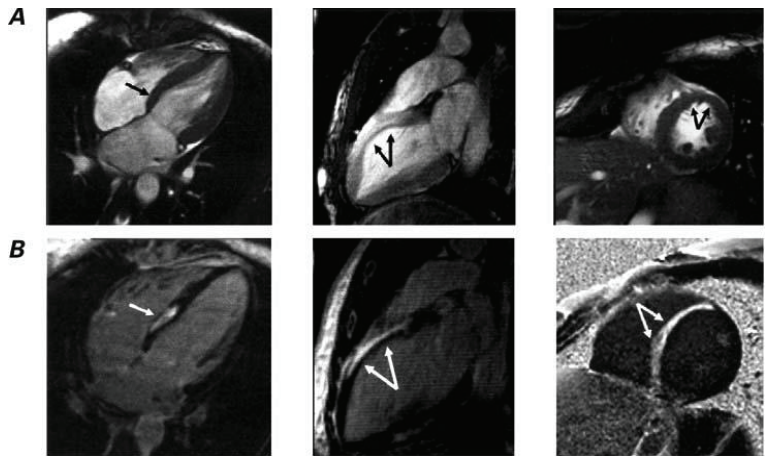
His EKG reinforced the cardiac enzymes' results, showing a clear alteration in ventricular repolarization and a poor R-wave progression in the anteroseptal wall [Picture 2]. First suspicion was that our patient was having a myocardial infarct, the latter which would be confirmed due to the enzyme values and EKG. The second suspicion was myocarditis. Also, his troponin T levels were as high as 1,770 ng/ml (reference values 0,000—0,025 ng/ml), which indicate heart tissue damage.



Pic. 2. EKG showing alteration in ventricular repolarization

Acute myocarditis may mimic acute myocardial infarction (AMI) when the patient has various combinations of chest pain, hemodynamic instability, ischemia-like electrocardiographic (ECG) changes, biochemical marker (troponin I and T and/or creatine kinase) changes, and segmental wall motion abnormalities at presentation. Myocarditis is an acute or chronic inflammatory disease of the myocardium which can be viral, postinfectious immune or primarily organ-specific autoimmune [10]. AMI must be considered in patients presenting with recent-onset cardiac failure or arrhythmia, though the onset of clinical symptoms may be vague and clinical features are heterogeneous, ranging from asymptomatic, generalized malaise, acute heart failure, dilated cardiomyopathy. In contrast, fulminant myocarditis is characterized by a distinct viral prodromal period, a rapid onset of symptoms, extensive haemodynamic compromise and marked myocardial inflammation. The formal differential diagnosis of AMI or acute myocarditis is based on positive findings of endomyocardial biopsy, which usually is considered the reference standard. However, this invasive procedure has several major drawbacks: first, the diagnostic sensitivity of endomyocardial biopsy strongly depends on the quality of the sample, and false-negative results can be observed when the sample is taken from a non-involved area [6]. As a matter of precaution and due to the high incidence of Chagas' disease in Brazil, he was also tested for Chagas' IgG — negative. Myocarditis was confirmed due to the already known viral infection, patient was put in vasoactive drugs treatment (Dobutamine). Also, as of rule, myocarditis can be suspected with all the mentioned above, that is, viral infections are the most common causes for myocarditis, and increased IgM against viruses known to cause such. It also must be said that the diagnosis of acute myocarditis is frequently empiric, and is made on the basis of the clinical presentation, electrocardiographic changes, elevated cardiac enzymes, and lack of epicardial co-

ronary artery disease. The diagnosis of acute myocarditis can also be confirmed with use of cardiac magnetic resonance imaging. The latter would be able to show anatomical imaging and an accurate assessment of functional parameters, but in this respect what is more important is its ability to characterize tissue. Presence of contrast enhancement (CE) indicates myocardial injury (i.e. scar, fibrosis) and T2-weighted images mark interstitial edema, known as an integral part of the inflammatory response [10]. An example of that kind of imaging is shown below [Picture 3].



Pic. 3. Myocarditis can mimic myocardial infarction.
MRI is the most non-invansive form for the differential diagnosis

The *Dengue Fever Shock Syndrome* (DFSS) presents a: *hemodynamic compound* — increase of vascular permeability, which leads to increased vascular tonus and subsequently increased vascular resistance; *a hypovolemic compound* — decreased intravascular tonus and can be associated, which is our case, with a *cardiac compound* (myocardial dysfunction). All of the three mentioned compounds occur simultaneously. What concerns the liver involvement overall, as he later would develop jaundice, even though it has been reported before, the pathogenic mechanisms are not yet fully elucidated. Some believe that it is related to combined interactions of the virus, the host and the duration of disease [7]. The virus may have a replication phase in hepatocytes, causing hepatic injury, stimulating apoptosis, microvesicular steatosis and the development of Councilman-Rocha Lima bodies, similarly to yellow fever infection and other viral hemorrhagic diseases. Increased liver volume in our patient was confirmed with an abdominal ultrasound: right lobe — 15,7; left lobe — 5,8; caudal lobe — 2,0.

Patient was finally diagnosed with DFSS (Dengue Fever Shock Syndrome — a complication of hemorrhagic dengue fever), cardiac insufficiency (myocarditis) and ischemic hepatitis, latter which was reinsured through hepatic enzymes results. Also, as a result of his cardiac condition, he was put on dialysis for acute renal failure — mainly due to the DFSS, that means, due to the decreased blood flow to his kidneys and due to large volumes of intravascular fluid that are lost into tissues, patient also presented oliguria. First measures were taken to restore circulating blood volume through fluid intake — which is the most important course of action for patient DFSS patients' stabilization. At this time, our patient was prescribed with Dobutamine (as already mentioned),

to his heart condition Norepinephrine. Paracetamol was used for symptom managing (500 g every 6 hours). It must the noted here that acetylsalicylic acid must not be prescribed, as it may cause hemorrhaging. For patients presenting nausea, antiemetic medications such as Metoclopramide may be aggregated to the course of treatment. He was put on O_2 saturation 35%. As with most viral hemorrhagic fevers, supportive care is the principal treatment approach.

Patient discharge. Patients must meet all five criteria below: 1) hemodynamic stabilization for 48 hours; 2) absence of fever for 48 hours; 3) visible improvement of the clinical picture; 4) normal hematocrit and stable for 24 hours; 5) platelets in elevation and above 50.000/mm³. Our patient fit all the criteria and overall progressed well during his hospital stay with the given treatment. On his 33rd day of hospital stay his hepatitis continued to regress. Patient was stable, with normal heart rate of 70 bpm; was discharged and recommended for future follow up.

Conclusions and differential diagnosis. As there is no licensed dengue vaccine, prophylactic measures may consist of repellents, house screening for dengue eggs on water, *Aedes aegypti* control. Healthcare authorities must keep control of endemic areas not only in order to prevent epidemics, but also to help diagnosing in those regions, as we know that relapsing fever may be confused with rickettsioses, malaria, typhoid, brucellosis, leptospirosis, rat-bite fever or meningococcemia depending on the epidemiologic circumstances. For differential diagnosis we must note that a rash that is hemorrhagic, particularly if associated with leukopenia and thrombocytopenia suggests dengue fever. In addition, the liver can also be prominently involved in systemic infection with viruses such as cytomegalovirus and Epstein-Barr virus. But the liver involvement with Dengue Shock Syndrome is characterized by centrilobular and midzonal hepatocellular necrosis with minimal inflammatory response, and the already mentioned Councilman Rocha-Lima bodies. Furthermore, the diagnosis of dengue is clinical (history + physical examination) made essentially by exclusion of other diseases. It is very important to stay alert whether the patient is not with meningococcal disease (meningitis or meningococcemia) or leptospirosis that are treatable with antibiotics. After the clinical diagnosis of dengue, some tests (hematocrit, platelet count) may provide useful information when analyzed by a doctor but do not confirm the diagnosis, since it also may be altered in various other infections. The confirmation of the diagnosis, if desired for any reason, can be done by serology (test that detects the presence of antibodies against Dengue virus), which starts to become reactive ("positive") from the fourth day of disease.

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ГЕМОРРАГИЧЕСКАЯ ЛИХОРАДКА ДЕНГЕ: КЛИНИЧЕСКИЙ СЛУЧАЙ (БРАЗИЛИЯ)

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Лихорадка денге (ЛД) является распространенной причиной арбовирусных инфекций в Южной Америке, принадлежащих к роду Flavovirus. Только в Форталезе, в 5-м по численности населения городе Бразилии, в 2011 году регистрировалось более 110 случаев заболевания лихорадкой денге в день [3].

Мужчина 50 лет, находящийся в сознании, поступил в Больницу Инфекционных Заболеваний Сао-Жозе с классическими симптомами лихорадки денге, на 9-й день от появления первых симптомов заболевания. ЛД редко рассматривается как причина острой печеночной недостаточности [4]. В данном описанном случае у больного наблюдалось поражение трех разных систем органов. У больного выявлены острая печеночная недостаточность, причиной которой был ишемический гепатит (такие ее причины, как острый вирусный гепатит, лептоспироз, малярия, синдром Рейеса были исключены), кардиомегалия и сепсис с явлениями септического шока. При лечении указанных осложнений наступило значительное улучшение клинической картины и биохимических показателей. После 33 дней пребывания в больнице больной был выписан из стационара.

Ключевые слова: лихорадка Денге, Flavivirus, инфекционные заболевания, вирусные геморрагические лихорадки, тропические болезни, Бразилия, Aedes Aegypti.