



Pathology of Dengue Fever- Autopsy Study in a Tertiary Care Hospital.

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ABSTRACT

Objective: To study gross and microscopic pathology in various organs in serologically proven dengue related deaths. **Materials & Methods:** Autopsies carried out in fatal dengue cases from January 2015 to December 2016 were analysed. **Results:** Complete autopsies were conducted in all 8 cases of dengue fatalities. Edema and intrapulmonary hemorrhage were significant pathologies in lungs. Acute tubular necrosis of kidney was noted in majority of cases. Hemorrhage in the gastrointestinal mucosa, hepatic necrosis and myocardial interstitial haemorrhage were occasionally observed. **Conclusion:** Dengue fever should be regarded as a multiorgan infection. Autopsy studies will enlighten pathology in different organs. A better understanding of changes in different organs in dengue fever will help in the management and prevent fatalities.

KEYWORDS: Dengue fever, Autopsy, Histopathology.

Introduction

Dengue is the most common arthropod borne viral illness in humans, transmitted by mosquitoes of the genus *Aedes*.⁽¹⁾ Dengue virus is a single stranded, non segmented positive sense RNA virus in flaviviridae family having four antigenically distinct serotypes 1-4.⁽²⁾

Clinical spectrum of dengue infection includes asymptomatic infection⁽³⁾, nonspecific febrile illness, classic dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS)⁽⁴⁾.

Manifestations in classic dengue fever include high fever, headache, retro-orbital pain, muscle and bone pains, weakness, vomiting, sore throat, altered taste sensation and maculopapular rash. Leucopenia, lymphopenia and thrombocytopenia are common findings in dengue fever.⁽⁴⁾ In Dengue Hemorrhagic Fever (DHF), vascular leakage results in hemoconcentration, serous effusions and haemorrhages (capillary fragility and thrombocytopenia) manifesting as petechial skin haemorrhages to life threatening gastrointestinal bleeding. In Dengue Shock Syndrome DHS progresses into circulatory failure (hypotension & shock)⁽⁴⁾

High index of suspicion, serodiagnosis, PCR and culture help to the confirm diagnosis of Dengue. Autopsy is carried out in very few Dengue fatalities. Studying pathological changes in different organs in fatal dengue cases will help in better understanding disease and management of affected patients.

The aim of this study was to describe the gross and histopathological changes in different organs in fatal dengue cases.

Materials & Methods

This study was carried out in a tertiary care hospital in Mumbai. 8 autopsy cases of dengue related deaths in year 2015 & 2016 were studied. All 8 cases were diagnosed dengue seropositive using rapid card test kits manufactured by SD Bioline. Clinical examination findings and investigations were obtained from hospital records. Autopsies were conducted after due consent from the

deceased's relatives. Thorough external and insitu examination of the body and detailed gross findings of the different organs was done. After adequate fixation, sections were taken from different organs, submitted for tissue processing and slides were prepared. H & E stained slides were studied and microscopic findings in different organs were noted.

Results

The 8 deceased, (5 males, 3 females) had age ranging between 4.5 to 65 years. All had fever with chills from 1 to 3 days duration. Other symptoms were pain in abdomen, vomiting, hematemesis, malena and altered sensorium. They deteriorated rapidly and died within 1 day of admission. 2 were positive for NS1, Ig G & M both, 5 were positive for NS1 only and 1 patient was positive for Ig G & M only by rapid immunochromatographic assay. Thrombocytopenia was present in 7 cases and 1 patient had normal platelet count. Liver function tests were deranged in 2 patients and in one patient SGPT was 3077 IU/LSGOT- 1580 IU/L, Total Bilirubin was 4.1mg/dl. Prothrombin time was elevated in 2 out of 5 patients. Serum creatinine was elevated in 5 out of 8 patients.

On gross examination, Cerebraledema was seen in 4 out of 8 patients. Cerebral surface showed widening of gyri and narrowing of sulci. Lung were either subcrepitant or were boggy voluminous with firm rubbery consistency. Liver showed subcapsular hemorrhage in 1 case. Splenomegaly was seen in 3 cases. Kidneys showed petechial haemorrhages in 2 cases. Stomach and intestinal mucosa showed congestion in 5 cases. One case showed mucosal petechial haemorrhages, 2 cases showed altered blood in bowel. Heart and pancreas were grossly unremarkable.

Microscopically, brain showed oedematous change in 5 cases and patchy parenchymal haemorrhages in 1 case (Figure 2). Lung showed oedema (4), Chronic passive venous congestion (3), interstitial pneumonia (1) and haemorrhage (4) (Figure 5). Liver showed ischemic necrosis (2) (Figure 1) and cirrhosis (1). Kidney showed cloudy change (3) and acute tubular necrosis (3). Mucosal

ischemic necrosis and sub mucosal haemorrhages were seen in 1 case each in intestine. Heart showed interstitial haemorrhage (Figure 4) and severe congestion in one case. Pancreas and spleen did not show any significant microscopic pathology.

Table 1: Gross findings in Dengue related deaths

Gross	P 262 15	P 347 15	P 477 15	P 523 15	P 524 15	P 473 16		P 483 16
Brain	Congestion	Edema	Edema	Congested	Edema	Congested	Edema	Congestion
Heart	Unremarkable (UR)	Petechial Hemorrhage pericardium	UR	UR	UR	UR	UR	UR
Lungs	Unremarkable (UR)	Hemorrhagic pleural effusion, Petechial hemorrhages	Boggy, Angry Red looking	Boggy, Edema	UR	Boggy, Angry Red looking	Boggy, Angry Red looking	Firm, rubbery, blood oozing on pressure
Liver	CPC	Capsular exudates	UR	Enlarged, fatty	UR	Enlarged, CPC	UR	Enlarged, Cholestatic
Spleen	Enlarged	UR	Enlarged	Enlarged	UR	Mushy	UR	Enlarged
Kidneys	Petechial Hemorrhages	Petechial Hemorrhages	Irregular scars	UR	UR	UR	UR	UR
GIT	Mucosa congested	Mucosal petechial hemorrhages, Serosalexudates	Congested	Congested	Congested with altered blood contents	Congested with altered blood content	Congested	Edematous

Table 2: Microscopic Findings in Dengue related deaths

Micro	P 262 15	P 347 15	P 477 15	P 523 15	P 524 15	P 473 16	P 476 16	P 483 16
Brain	Edema	Congested	Cerebral H'ages	Congestion & Edema	Congestion	Congested & Edema	Congested & Edema	Congested & Edema
Heart	UR	UR	Hypertrophy	UR	UR	Hypertrophy	Interstitial H'ages	Hypertrophy
Lungs	Edema	Pulmonary subpleural h'age	Edema & CPC	Edema & Pulmonary h'age	CPC, Fibrin thrombi in capillaries	Edema & pulmonary h'age, TB pneumonia	pulmonary h'age	Interstitial Pneumonia
Liver	Sinusoidal congestion	CPC	Cirrhosis	Ischemic necrosis, fatty change	Sinusoidal congestion	Sinusoidal congestion	Sinusoidal congestion	Hemorrhagic necrosis, Fatty liver, Cholestasis
Spleen	congested	congested	congested	congested	congested	congested	congested	congested
Kidneys	ATN	ATN, subcapsular h'ages	Cloudy Diabetic nephropathy	Cloudy change	ATN	Cloudy change	Congested	ATN

GIT	UR	Mucosa-Ischemic necrosis, Serosa-Exudate	Congested	Congestion	Mucosa-Ischemic necrosis	UR	Congested & Edema	Congestion
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Discussion

Dengue is a systemic viral infection causing multiorgan pathology. Liver is the most commonly affected organ in Dengue Hemorrhagic Fever. (5) Liver shows varying histological changes as microvesicularsteatosis, hepatocellular necrosis. In dengue fever, acute liver failure predisposes to hemorrhage, DIC and encephalopathy which can be life threatening. (6,7) In our study 3 of 8 cases showed liver pathology. One case showed centrilobular necrosis, one showed hemorrhagic necrosis with cholestasis in a background of chronic passive venous congestion and one case showed submassive hepatic necrosis. These cases with liver pathology showed hemorrhagic manifestations in other organs like gastrointestinal bleeding, intrapulmonary hemorrhage and intracerebral hemorrhage.

Lung involvement in Dengue fever is manifested as alveolar congestion, septal haemorrhages, diffuse alveolar haemorrhages and pleural effusions. (8,9,10) Clinically the patients with dengue hemorrhagic fever can present as ARDS. In our study all 8 patients showed significant lung pathology. Histology showed edema (4 /8 cases), intraalveolar haemorrhages (4/8 cases), changes of CPC (3/8 cases), one case each showed interstitial pneumonia and tuberculous bronchopneumonia. Fibrin thrombi were seen in capillaries in 1 case (Figure 3). Siderophages, foreign body giant cells were seen around terminal airways with siderophages also present in their lumen suggesting aspiration of gastrointestinal hemorrhage as intestinal mucosa showed hemorrhagic necrosis in this case.

The main lesion in kidney was Acute Tubular Necrosis (ATN) of proximal convoluted tubules caused by ischemia due to severe hypovolemic shock with significant blood loss. (11) ATN is characterised by sloughing of necrotic cells, loss of basement membrane mainly in proximal convoluted tubules with formation of casts of cellular debris. In our study 4 cases showed ATN. All these cases showed elevation in serum BUN & Creatinine levels. The cause of ATN can be attributed to hypovolemic shock due to plasma leakage.

Brain showed edema and congestion in majority of cases. There was intraparenchymal hemorrhage only in one case. Study by Mishra et al (12) showed intra cerebral haemorrhages in significant number of cases. Encephalitis has been reported though it is rare (13) and was not seen in any of our cases.

In all our cases spleen showed red pulp congestion. Study done by Aung- Khin M et al (14) about changes in the tissues of the immune system has shown depletion of cells in the periarterial lymphatic sheaths and paracortical areas of lymph nodes in dengue hemorrhagic fever.

Cardiac complications of dengue are rare (15) Dengue patients can manifest a wide spectrum of cardiac changes which include myocarditis, pericarditis and cardiac rhythm disturbances. (16,17,18) One case showed severe interstitial congestion and patchy haemorrhages. Majority of patients did not show any cardiac clinical manifestations, ECG changes or serum cardiac biomarker elevations. One case showed gastrointestinal mucosal hemorrhage. Literature has documented various mechanisms of hemorrhage like thrombocytopenia, platelet dysfunction or microvascular injury. (19)

Conclusion

Due to multiorgan pathology in dengue fever, the patients can present with a wide range of clinical manifestations posing difficulties in diagnosis and treatment. In Dengue related deaths, autopsy should be recommended and gross and microscopic

findings should be recorded. This will help in better understanding of pathogenesis of disease and can help in management.

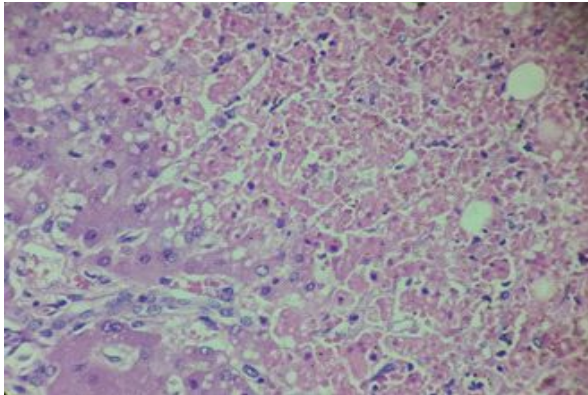


Figure 1, H&E 10X, Liver showing Hemorrhagic Necrosis

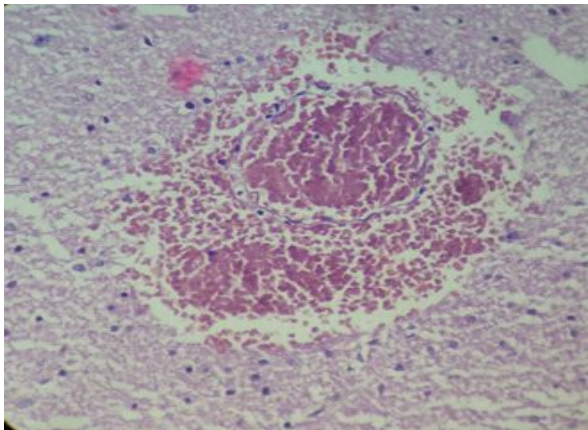


Figure 2, H&E 10X, Cerebral haemorrhage

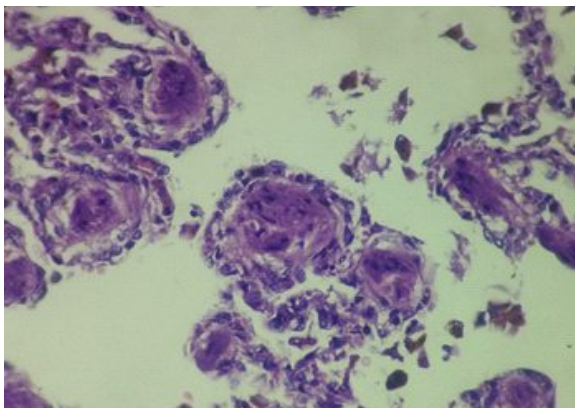


Figure 3, H&E, 40X, Fibrin Thrombi in Pulmonary Capillaries.

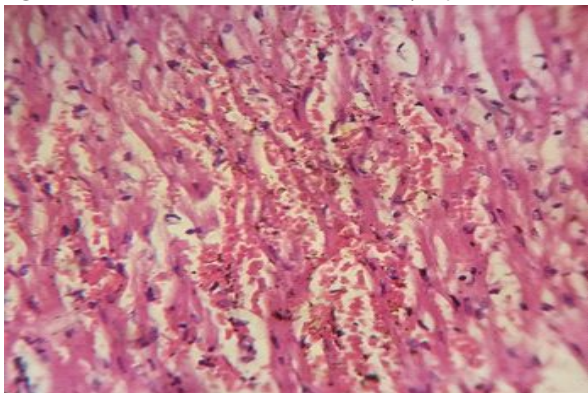


Figure 4, H&E, 10X, Myocardial Interstitial Hemorrhage.

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