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## IMPORTANCE OF PULMONARY COMPLICATIONS IN DENGUE

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### ABSTRACT

Dengue is a major vector-borne disease caused by four serotypes of dengue virus. Human organs such as liver, spleen and lymph nodes have been found to contain inactivated dengue virus. Although dengue virus has been reported to infect and replicate in human primary lung epithelium, impact of different serotypes on human lungs has been poorly understood. We strongly feel that pulmonary complications due to dengue virus should be seriously viewed for better treatment and management of dengue cases.

**Keywords:** *Dengue, Pleural Effusion, Pulmonary Edema, Pulmonary Dysfunction*

### INTRODUCTION

Dengue is considered to be the most important arthropod-borne disease in humans and is caused by any of the four dengue virus (DENV-1-4) serotypes. Dengue is caused by a single-stranded RNA virus belonging to the genus *Flavivirus*. It is one of the most important and notorious arbo-viral infection prevalent in tropical and sub-tropical regions around the world. DENV may cause the potentially fatal disease named dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). The incidence of dengue has grown dramatically around the world in recent decades. Over 2.5 billion people over 40% of the world's population are now at risk from dengue. WHO currently estimates there may be 50–100 million dengue infections worldwide every year. An estimated 500 000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die (<http://www.who.int/mediacentre/factsheets/fs117/en/>)

The involvement of different organs by dengue virus has been inadequately documented. Evidence of dengue replication in lymph node, splenic and pulmonary macrophages has been reported from the biopsy and necropsy of the patients with dengue infection (Jessie *et al.*, 2004). Liver, spleen and mesenteric lymph nodes have been reported to contain primarily inactivated virus (Rosen *et al.*, 1999). Viral antigens have also been demonstrated in macrophages and vascular endothelium in the lungs. Studies on identification of potential receptor molecules / specific dengue virus binding proteins in human lung cells are being encouraged. Although dengue virus has been reported to infect and replicate in human primary lung epithelium (Lee *et al.*, 2007), interaction of different serotypes of dengue virus in physiological functioning of lungs has not been well elucidated. In this review, the importance of viewing pulmonary complications for better treatment of management of dengue cases has been discussed.

### **Impacts on Various Organs by Dengue Virus**

Dengue infection may cause different kinds of impacts on various organs like liver, heart, epidermal keratinocytes, lungs etc (Dalrymple and Mackow, 2012). The infection could cause pleural-pulmonary complications. This may be due to an increase in vascular permeability induced by the virus inflammatory response (Isea-Dubuc *et al.*, 2008). When the infection become severe, dengue virus could even damage the vital organs and thereby cause morbidity and mortality. In dengue patients, plasma leakage is important and should be managed carefully to prevent or reverse hypovolemic shock. Non-cardiac pulmonary oedema is a common complication of fluid replacement in patients with dengue and profound plasma leakage. During the phase of plasma leakage, pleural effusions (usually right side) and ascites are common. There are several limitations in the investigation on the involvement of lungs in dengue infection and this might be the cause of lack of detailed studies on this aspect.

The major target tissues for dengue virus infection have been difficult to determine but virus has been isolated from human blood, lymph node, bone marrow, liver, heart, and spleen. Activated viral-specific T

### **Research Article**

cells may bind specific receptors on virus-infected cells and induce their apoptosis. Some T cells may also enter the lungs and can cause damage and either undergo apoptosis or leave the lungs. They could also produce a range of cytokines/chemokines, and cause damage to lungs at a distance from the site of immune activation

#### **Dengue Virus on Endothelial Cells**

The respiratory epithelium is also a target for dengue virus. It has been reported on the involvement of the respiratory epithelial cell with dengue infection and it has been associated with expression of IL-6 through a NF- $\kappa$ B-dependent pathway, and expression of chemokine RANTES (Lee *et al.*, 2007; Louie *et al.*, 2009). As both the dengue and H1N1 2009 infections are known etiologic factors of ARDS, concomitant infection with both was expected to cause severe ARDS in this patient (Borthakur *et al.*, 2011). Dengue haemorrhagic fever can result in acute respiratory distress syndrome (ARDS) (Lum *et al.*, 1995; Thong, 1998; Sen *et al.*, 1999). It has been suggested that endothelial cells can support the replication of dengue virus, liberation of several inflammatory mediators including an interleukin 8 (IL-8) and RANTES (Avirutnan *et al.*, 1998; Juffrie *et al.*, 2000). These substances are capable to enlist neutrophils and to promote ascular permeability increase. The recruitment of polymorpho-nuclear cells that occurred in a higher number in a later period of infection has been verified. The recruitment of these cells, probability is due to the release of IL-8 and RANTES by activated endothelial cells (Lee *et al.*, 2007).

Dengue virus antigen has been found in alveolar lining cells of the lung. Increased permeability of the alveolar-capillary membrane results in the oedema in the alveoli and interstitial spaces which lead to pulmonary dysfunction (Lum *et al.*, 1995). Dengue shock syndrome is reported to be the third leading cause of ARDS in the paediatric intensive care setting in a dengue endemic area (Goh *et al.*, 1998). Early restoration of adequate tissue perfusion is critical to prevent progression of dengue shock syndrome to ARDS. However, equal care must be exercised to avoid excessive fluid infusion after adequate volume replacement because fluid overload may result in ARDS. This complication requires early recognition and management for good results. Pulmonary haemorrhage with or without haemoptysis has also been reported in DHF (Liam *et al.*, 1993; Setlik *et al.*, 2004). The incidence of pulmonary manifestations is high among the complicated cases of dengue fever (DHF & DSS) and can be used as an indicator of serious presentation (Mohamed *et al.*, 2013).

Lung tissue showed some inflammatory cells and nuclear debris inside alveolar spaces. Passive congestion of the alveolar wall vessels was observed. In a study carried out with immune-compromised mice, the replication of DENV was verified in pulmonary tissue by titulation of cell cultures inoculated with a tissue macerate (Hotta *et al.*, 1981)). Although scarce, the dengue fever can induce pleural pulmonary complications. This may be due to an increase in vascular permeability induced by the virus inflammatory response (Isea-Dubuc *et al.*, 2008).

#### **Other Complications by Dengue Virus**

Other complications include non-cardiogenic pulmonary oedema, ARDS, hemorrhage-hemoptysis, platelet deficiency, pneumonitis, acute respiratory failure. These complications usually coincides with plasma leakage syndrome and thrombocytopenia, increase WBC Counts, increased liver enzymes. Generally there are progressive changes in chest X-Ray in first week, with normalization of chest X-Ray by day 14. Infiltration seen in dengue patients is generally because of bacterial infection or unknown mechanism. Pleural effusions are mainly transudative caused mainly by imbalance in hydrostatic and oncotic pressures mainly non-pulmonary lung, non-pleural factors. Non cardiogenic pulmonary oedema is a common complication of fluid replacement in dengue patients. Avoidance of excessive fluid infusion after adequate volume replacement must be monitored because fluid overload may result in ARDS (Gulati and Maheswari, 2007). Haemorrhage may be multifactorial because of vasculopathy or platelet dysfunction, blood coagulation defects (Kumar *et al.*, 2013).

Lung tissue showed interstitial pneumonia and mononuclear cells, interseptal oedema, hyperplasia, and hypertrophy of the bronchiolar epithelial cells. Dengue virus-2 led to a transient inflammatory process, but caused focal alterations of the blood-exchange barrier (Barth *et al.*, 2006).

### **Research Article**

During dengue virus infection, dengue virus (or viral antigen) has been detected in pulmonary macrophages and pulmonary endothelial cells (Jessie *et al.*, 2004). In fatal cases of dengue, histopathological findings include interstitial inflammation and haemorrhage, alveolar fluid and protein (including fibrin), and lung haemorrhage. Hypoxemia with a widened alveolar-arterial oxygen gradient is common in patients with severe dengue. Nevertheless, the effects of dengue virus infection on the lung are not completely understood and poorly appreciated (Mahajan *et al.*, 2013)

#### **Dengue Virus and Macrophage**

Histological analysis of lung tissues of dengue patients revealed interstitial pneumonia associated with vascular congestion, rare focal zones of parenchymal haemorrhage, increase of alveolar macrophages number, recruiting of platelets mononuclear, and polymorpho-nuclear cells (Barreto *et al.*, 2007). Similar injuries have also been observed in necropsies of human pulmonary tissues of dengue fatal cases (Burke *et al.*, 1988; Miagostovich *et al.*, 1997). In the ultra-structural analysis of alveolar macrophages of infected mice by the intravenous and intra-peritoneal routes, the presence of dengue virus-like particles inside vesicles the rough endoplasmic reticulum and Golgi complex were observed suggesting viral replication (Bareto *et al.*, 2007). Lung tissue showed some inflammatory cells and nuclear debris inside alveolar spaces. Passive congestion of the alveolar wall vessels was observed. Macrophages are thought to originate from hematopoietic stem cells (HSCs) during development and reside in various tissues such as Kupffer cells in the liver, microglia in the brain, alveolar macrophage in the lungs, osteoclast in the bone, and in lymph nodes and other tissues. Recent studies reveal that granulocyte macrophage colony-stimulating factor (GM-CSF) is influential skewing macrophage differentiation into distinct phenotypes. Understanding of different activations of inflammasome in macrophage subsets may help to illustrate the pathogenesis of dengue fever and dengue virus- induced lethal diseases (Wu *et al.*, 2013)

#### **Acute Respiratory Distress Syndrome (ARDS) and Dengue Virus**

ARDS is a syndrome of inflammation and increased permeability associated with a constellation of clinical, radiologic, and physiologic abnormalities unexplained by elevations in left atrial or pulmonary capillary pressure. Acute respiratory failure seen in dengue patients is a common complication of sepsis/combination bacterial infection. Risk factors for acute respiratory failure include decreased immunity and co-morbidity due to increased age, pressure of multiple organ failure, increased risk in patient with UGI bleedings, sepsis, increased AST, increased in ALT, and increased BUN, increased creatinine with acute renal failure (Mahajan *et al.*, 2013). Acute renal failure generally precedes acute respiratory failure. The other possible complications are combination bacterial infection, acute hepatic failure, hypovolumic shock, dengue encephalitis. Excessive plasma leakage may result in acute renal failure also precipitated by massive active haemorrhage. Dengue encephalopathy is a rare but recognized cause of febrile encephalopathy with spectrum ranging from clouding of consciousness (1-4%) to mononeuropathy, polyneuropathy, Gui 1 lan Barre Syndrome (GBS). Pathological impacts include hypotension cerebral oedema, micro vascular frank haemorrhage and hyponatremia. In DHF and DSS, pleural effusions may correlate with disease severity. Dengue hemorrhagic fever should be considered in the differential diagnosis of a patient with fever, haemoptysis, and diffuse pulmonary infiltration. The high-resolution CT findings of dengue hemorrhagic fever consist of bilateral areas of consolidation with air bronchogram and ground-glass opacities, and bilateral pleural effusions (Marchiori *et al.*, 2009). Dengue hemorrhagic fever is characterized by an increase in capillary permeability, which results in fluid extravasations (pleural effusion, ascites) and haemostatic changes, including decreased platelet levels near the time of defervescence and hemorrhagic manifestations (Marchiori *et al.*, 2009). The presence of dengue virus and its antigens has been reported in heart, liver, spleen, lymph node and lungs but the effect of this virus on these organs has been little studied especially on lungs. Further, there are scarce studies on the impact and complications caused by dengue virus in human lungs. Elaborate studies should be encouraged to investigate the pathogenesis of dengue virus in human lungs.

#### **Co-occurrence of Pathogens with Dengue Virus**

Some micro-organisms have been identified as occurring simultaneously with dengue virus infection. Among them, one can mention *Escherichia coli*, *Salmonella* sp., *Streptococcus pneumoniae*,

## **Research Article**

*Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, *Shigella sonnei*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Enterococcus faecalis*, *Moraxella lacunata*, *Staphylococcus aureus*, *Roseomonas* sp., *Haemophilus influenzae*, *Candida tropicalis*, and *herpes viruses* (Araújo et al., 2010). Clinicians should be very vigilant to unusual manifestations of dengue fever, which may signalize a concomitant infection by other microorganisms, mainly bacteria. The co-infection between dengue and naïve tuberculosis shows that both the microbes share lungs and the concurrent infection between dengue and tuberculosis is possible and should be kept in mind while treating such co-infections. Interaction between dengue and tuberculosis has also been described in another study (Joob and Wiwanitkit, 2013). Of late, there are reports of Adult Respiratory Distress Syndrome [ARDS] with Dengue Fever (Sen et al., 1999; Wang et al., 2007; Devarajan et al., 2008). There are very few studies showing this complication of dengue infection. This could result in a lack of widespread awareness of ARF (Acute Respiratory Failure) due to ARDS in dengue patients (Mohamed et al., 2013).

During the pandemic of the novel H1N12009 influenza, the outbreaks of dengue virus infections also occurred in many geographic locations, which were experiencing the pandemic of the H1N12009. As both the viruses are circulating in the same community, at the same time, in many locations, there may be the likelihood of people being afflicted by concomitant infection with both the viruses. Clinical status in case of concomitant infection with H1N1 and dengue should be cautiously interpreted. Although the severity of H1N1 may be clinically less obvious because of lesser immune response due to the immune suppression by the dengue virus, both the virus can cause some specific organ damage, which needs to be evaluated timely. Severity of H1N1 in a patient with dengue should not only be clinically evaluated but also by laboratory tests for viral load (Borthakur et al., 2011).

It has been found that previous viral infections of the lung may worsen COPD by stimulating a particular type of lung cell that over-activates the immune system. Respiratory viral infection may lead to an increase in lung epithelial progenitor cells that are programmed for increased production of IL-33 (<http://outlook.wustl.edu/2013/oct/copd>).

Dengue virus NS1 preferentially binds to cultured human microvascular compared to aortic or umbilical cord vein endothelial cells. This binding specificity was confirmed in situ as dengue virus NS1 bound to lung and liver but not intestine or brain endothelium of mouse tissues. Differential binding of soluble NS1 by tissue endothelium and subsequent recognition by anti-NS1 antibodies could contribute to the selective vascular leakage syndrome that occurs during severe secondary dengue virus infection (Avirutnan et al., 2007).

## **CONCLUSION**

Early recognition and prompt initiation of appropriate supportive treatment are often delayed resulting in unnecessarily high morbidity and mortality. Judicious fluid administration is necessary to avoid respiratory distress secondary to massive pleural effusions/ascites or pulmonary edema. Patients who develop massive pleural effusions or ascites require prolonged hospitalization for observation. Repeat ultra-sonography on the fifth to seventh days detected pleural effusion in a significantly higher number of patients with dengue fever.

Differential diagnosis should be made with proper care to rule out the involvement of lungs in dengue and appropriate supportive treatment must be given to the dengue affected patients so as to reduce risk due to different forms of dengue fever. Further studies are to be undertaken on the interaction and effect of different serotypes of dengue virus on various parts and physiological functioning of lungs. This would be very helpful for better diagnosis and appropriate treatment for serious complications in lungs due to dengue virus.

## **REFERENCES**

Araújo SA, Moreira DR, Ribeiro Veloso JM, Silva JO, Reis Barros VLS and Nobre V (2010). Case Report: Fatal Staphylococcal Infection following Classic Dengue Fever. *American Journal of tropical Medicine and Hygiene* **83** 679–682.

### **Research Article**

- Avirutnan P, Malasit P, Seliger B, Bhakdi S and Husman M (1998).** Dengue virus infection in human endothelial cells leads to chemokine production, complement activation and apoptosis. *Journal of Immunology* **161** 6338-6346.
- Barreto DF, Takiya CM, Schatzmayr HG, Nogueira RMR, Farias-Filho JC and Barth OM (2007).** Histopathological and ultrastructural aspects of mice lungs experimentally infected with dengue virus serotype 2. *Memorias instituto oswaldo cruz, Rio de Janeiro* **102** 175-182.
- Barth OM, Barreto DF, Paes. MV Takiya CM, Pinhao AT and Schatzmayr HG (2006).** Morphological studies in a model for dengue-2 virus infection in mice. *Memorias instituto oswaldo cruz, Rio de Janeiro* **101** 905-916.
- Borthakur B, Panwar D and Pawa M (2011).** Viral co-infection with dengue and H1N1 virus in a critical care setting. *Journal of Anaesthesiology and Clinical Pharmacology* **27** 236–238.
- Borthakur B, Panwar D, Garg R and Pawar M (2011).** Viral co-infection with dengue and H1N1 virus in a critical care setting. *Journal of Anaesthesiology and Clinical Pharmacology* **7** 236–238.
- Burke DS, Nisalak A, Johnson DE and Scott RM (1988).** A prospective study of dengue infections in Bangkok. *American Journal of Tropical Medicine and Hygiene* **38** 172-180.
- Dalrymple NA and Mackow ER (2012).** Endothelial cells elicit immune-enhancing responses to dengue virus infection. *Journal of Virology* **86** 6408-15.
- Dengue and severe dengue.** Available: <http://www.who.int/mediacentre/factsheets/fs117/en/>
- Devarajan TV, Prashant PS, Mani AK, Victor SM and Khan PS (2008).** Dengue with ARDS. *Journal of Indian Academy of Clinical Medicine* **9** 146-149.
- Gohet AYT, Chan PWK, Lum LCS and Roziah M (1998).** Incidence of acute respiratory distress syndrome: a comparison of two definitions. *Archives of Diseases in Child* **79** 256-59.
- Gulati S and Maheswari A (2007).** Atypical manifestations of dengue. *Tropical Medicine and International Health* **12** 1087-1095.
- Hotta H, Murakami I, Miyasaki K, Takeda Shirane H and Hotta S (1981).** Innoculation of dengue virus into nude mice. *Journal of General Virology* **152** 71-76.
- Isea-Dubuc JO, Vargas C and Suarez JA (2008).** Pleuro-pulmonary complications in dengue hemorrhagic fever free to view. *CHEST* **134**.
- Jessie K, Fong MY, Devi S, Lam SK and Wong KT (2002).** Localization of Dengue Virus in Naturally Infected Human Tissues, by Immunohistochemistry and in Situ Hybridization. *Infectious Diseases* **189** 1411-1418.
- Job B and Wiwantikit N (2013).** Concurrent dengue infection in a patient with pulmonary tuberculosis: the first world report. *Journal of Thoracic Diseases* **5** 3.
- Juffrie M, Meer DM, Hack CE, Haasnoot K, Sutaryo N, Veerman AJ and Thijs LG (2000).** Inflammatory mediators in dengue virus infection in children: interleukin-8 and its relationship to neutrophil degranulation. *Infectious Immunology* **68** 702-707.
- Kumar N, Gadpayle AK and Trisal G (2007).** Atypical respiratory complications of dengue fever. *Asian Pacific Journal of Tropical Medicine* **6** 839-840.
- Lee YR, Su CY, Chow NH, Lai WW, Lei, HY, Chang CL, Chen SH, Lin YS, Yeh TM and Liu HS (2007).** Dengue viruses can infect human primary lung epithelia as well as lung carcinoma cells and can also induce the secretion of IL-6 and RANTES. *Virus Research* **126** 216-25.
- Liam CK, Yap BH and Lam SK (1993).** Dengue fever complicated by pulmonary hemorrhage manifesting as hemoptysis. *Journal of Tropical Medicine and Hygiene* **96** 197–200.
- Louie JK, Acosta M, Winter K, Jean C, Gavali S and Schechter R et al., (2009).** Factors associated with death or hospitalization due to pandemic 2009 influenza A (H1N1) infection in California. *JAMA* **302** 1896-902.
- Lum LCS, Thong MK, Cheah YK and Lam SK (1995).** Dengue-associated adult respiratory distress syndrome. *Annals of Tropical Paediatrics* **15** 335–339.
- Mahajan SN, Rathi NP and Acharya S (2013).** ARDS in dengue infection-A case series. *Indian Journal of Medicine and Health Care* **2** 2278-2966.

**Research Article**

- Marchiori E, Ferreira JLN, Bittencourt CN, Neto CAA, Zanetti G, Mano CM, Santos AA and Vianna AD (2009).** Pulmonary hemorrhage syndrome associated with dengue fever, High-resolution computed tomography findings: a case report. *Orphanate Journal of Rare Diseases* **4** 8.
- Miagostovich MP, Ramos RG, Nicol AF, Nogueira RMR, Cuzzi-Maya T, Oliveira AV, Marchevsky RS, Mesquita RP and Schatzmayr HG (1997).** Retrospective study on dengue fatal cases. *Clinical Neuropathology* **16** 204-208.
- Mohamed NA, El-Raouf EA and Ibraheem HA (2013).** Respiratory manifestations of dengue fever in Taiz-Yemen. *Egyptian Journal of Chest Diseases and Tuberculosis* **62** 319-323.
- Rosen L, Drouet MT and Deubel V (1999).** Detection of dengue virus RNA by reverse transcription-polymerase chain reaction in the liver and lymphoid organs but not in the brain in fatal human infection. *American Journal of Tropical Medicine and Hygiene* **61** 720-4.
- Sen MK, Ojha UC and Chakrabarti S et al., (1999).** Dengue Hemorrhagic fever (DHF) presenting with ARDS. *Indian Journal of Chest Diseases and Allied Sciences* **41** 115-119.
- Setlik RF, Ouellette D and Morgan J et al., (2004).** Pulmonary hemorrhage syndrome associated with an autochthonous case of dengue hemorrhagic fever. *Southern Medical Journal* **97** 688-691.
- Thong MK (1998).** Dengue Shock Syndrome and acute respiratory distress syndrome. *Lancet* **352** 1712.
- Viral infections linked to COPD. Discovery points to new therapeutic targets. Available at: [Http://outlook.wustl.edu/2013/oct/copd](http://outlook.wustl.edu/2013/oct/copd)**
- Wang CC, Liu SF, Liao SC, Lee IK, Liu JW and Lin AS et al., (2007).** Acute respiratory failure in adult patients with dengue virus infection. *American Journal of Tropical Medicine and Hygiene* **77** 151-158.
- Wu MF, Chen ST and Hsieh SL (2013).** Distinct regulation of dengue virus-induced inflammasome activation in human macrophage Subsets. *Journal of Biomedical Science* **20** 3.