J Bras Pneumol. 2020;46(1):e20190246
http://dx.doi.org/10.1590/1806-3713/e20190246

Pulmonary manifestations of dengue

Edson Marchiori[1,a], Bruno Hochhegger[2,b], Gláucia Zanetti[1,c]

TO THE EDITOR:

Dengue is an arthropod-borne viral disease transmitted to humans through the bites of infected female mosquitoes of the *Aedes* genus. The dengue virus (DENV) belongs to the Flaviviridae family, and humans can be infected with any of the four antigenically distinct serotypes (DENV 1-4).[1-7] The prevalence of DENV infection has increased dramatically in recent decades; the disease is now endemic in > 100 countries worldwide. The global resurgence of dengue is thought to be due to the failure to control *Aedes* spp. populations, uncontrolled urbanization, population growth, climate change, and increasing numbers of international travelers.[1,2,4,5,7] In Brazil, the number of cases of dengue fever reported in January-August 2019 was approximately 600% higher than that reported during the same period in 2018. As of August 2019, the disease had caused 591 deaths, compared with only 141 for the same period in 2018.[8]

According to the 2009 World Health Organization guidelines,[2] patients with dengue are categorized as having the non-severe form (subdivided into those with warning signs and those without) or the severe form. Patients with non-severe dengue without warning signs are defined as those who live in or have travelled to dengue-endemic areas and have fever, together with at least two of the following: nausea, vomiting, rash, pain, leukopenia, and positive tourniquet test results. Patients with non-severe dengue with warning signs are defined as those who present with all of the above, plus any of the following additional symptoms: abdominal pain or tenderness, persistent vomiting, fluid accumulation (pleural effusion or ascites), mucosal bleeding, lethargy, restlessness, liver enlargement > 2 cm, and an increase in hematocrit concurrent with a rapid decrease in the platelet count. Severe dengue is characterized by at least one of the following: severe plasma leakage leading to shock, with or without fluid accumulation with respiratory distress, and severe bleeding or severe involvement of organs (liver, central nervous system, heart, or other).[1-4,7]

Dengue has a wide spectrum of clinical signs and symptoms, ranging from asymptomatic infection to severe, lethal manifestations. The disease usually presents as acute fever with headache, rash, myalgia, arthralgia, retro-orbital pain, prostration, lymphadenopathy, and dry cough. Hemorrhagic manifestations in patients with dengue are usually mild, most commonly consisting of scattered tiny petechiae on the skin or submucosa and ecchymoses. Variable frequencies of respiratory symptoms have been reported in patients with dengue; the symptoms are generally mild and affect mainly the upper airway.[5,7,9-11] Pulmonary complications are less common and can present as pleural effusion, pneumonitis, noncardiogenic pulmonary edema, acute respiratory distress syndrome, and pulmonary hemorrhage. Such complications coincide with capillary leak syndrome and thrombocytopenia. Dyspnea may occur due to pleural effusion (most frequently), acute respiratory distress syndrome, pulmonary hemorrhage, pneumonia, or shock. Diffuse alveolar hemorrhage is rare, and is typically related to severe—often fatal—forms of the disease. Hemoptysis has been reported in 1.4% of DENV infections.[5-7,9,10]

The early diagnosis of dengue can be established provisionally by clinical observation and readily available laboratory tests. In general, laboratory findings of dengue include neutropenia followed by lymphocytosis, the presence of atypical lymphocytes, and moderate to marked thrombocytopenia with concurrent hemoconcentration.[5,7,11]

Diagnostic options include assays to detect DENV, its components (genome and antigen), or the host response to the virus. Laboratory confirmation can be made by detecting the viral genomic sequence through RT-PCR or the presence of DENV nonstructural protein 1 (NS1) antigen though immunoassay in a single acute-phase serum specimen obtained early (less than five days after fever onset). During the febrile phase, the detection of viral nucleic acid in serum by RT-PCR or of DENV-expressed soluble NS1 by ELISA or the lateral-flow rapid test is sufficient for a confirmatory diagnosis. Therefore, less than five days after fever onset, RT-PCR is indicated, and serology (IgM ELISA) should be performed only after day 5. A finding of IgM seroconversion (≥ 4-fold increase in the antibody titer) between paired samples is considered to be confirmatory; IgM detection in a single specimen from a patient with a clinical syndrome consistent with dengue is used widely to establish a presumptive diagnosis.[2,4,7,9]

The most commonly observed chest imaging finding in dengue is pleural effusion, which is often bilateral. When unilateral, it usually occurs on the right. Parenchymal abnormalities, including ground-glass opacities and consolidations, are less common, have no specific distribution pattern, and can be accompanied by interlobular septal thickening and nodules, representing edema or pulmonary hemorrhage (Figure 1).[6,7,9-11]

We had the opportunity to review the CT findings of 9 patients with severe dengue confirmed by serology. The most common CT findings were multifocal ground-glass opacities, which were seen in 8 patients (88.9%). A predominance of central (perihilar) lung involvement was

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
a. http://orcid.org/0000-0001-8797-7380; b. http://orcid.org/0000-0003-1984-4636; c. http://orcid.org/0000-0003-0261-1860

BY-NC © 2020 Sociedade Brasileira de Pneumologia e Tisiologia

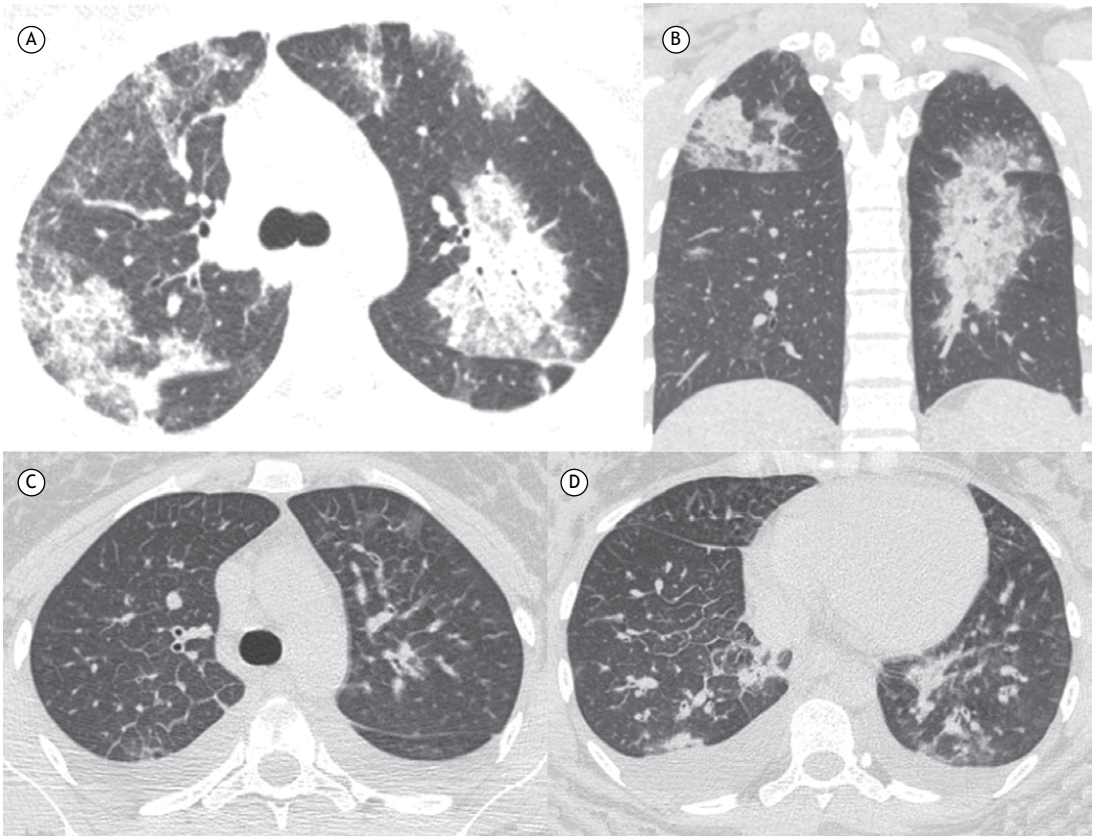

Figure 1. Two patients diagnosed with dengue. In A and B, a 37-year-old woman with severe dengue and pulmonary hemorrhage. Axial CT scan (A) and coronal reconstruction (B), showing bilateral multifocal areas of consolidation and ground-glass opacity. In C and D, a 51-year-old woman with severe dengue and findings of pulmonary edema. Axial CT scans of the upper and lower lobes (C and D, respectively), showing bilateral peribronchovascular and interlobular septal thickening, together with multifocal areas of mild consolidation and ground-glass opacity in both lungs. Note also the bilateral pleural effusion.

observed in 4 patients (44.4%). Four patients (44.4%) also had areas of consolidation. The consolidations were accompanied by ground-glass opacities in 3 patients (33.3%); consolidations only were observed in 1 (11.1%). A crazy-paving pattern and smooth interlobular septal thickening were observed in 1 patient (11.1%) each. Bilateral pleural effusion was observed in 5 patients (55.6%). In all of the patients, the abnormalities were bilateral and diffuse (Figure 1).

Drawing clinical and radiological distinctions between dengue and other infections that cause diffuse pulmonary hemorrhage may be challenging. In immunocompetent patients, the most important infectious diseases for differential diagnosis include influenza A (H1N1), leptospirosis, malaria, and hantavirus pulmonary syndrome. Those conditions can occur in similar epidemiological contexts, increasing the diagnostic challenge.[6,7]

Morphologically, lung tissue from patients with dengue shows interstitial edema and pneumonia, accompanied by focal or diffuse zones of alveolar congestion/hemorrhage and an increased number of alveolar macrophages, as well as the recruitment of platelets, mononuclear cells, and polymorphonuclear cells. Hyaline membranes may also be found.[6,7,9,11]

No specific treatment for dengue is available. However, careful clinical management frequently saves the lives of patients with pulmonary hemorrhage. With appropriate intensive supportive therapy, mortality may be reduced to < 1%.[2,5,7]

In conclusion, lung abnormalities are uncommon in dengue, and imaging findings probably reflect increased vascular permeability. Dengue should be considered in the differential diagnosis of patients with fever, hemoptysis, and diffuse pulmonary infiltration. The most common imaging findings in dengue are bilateral areas of ground-glass opacity or consolidation and bilateral pleural effusions. Recognition of these findings may help clinicians initiate prompt treatment and prevent mortality.

REFERENCES

1. Nunes PCG, Daumas RP, Sánchez-Arcila JC, Nogueira RMR, Horta MAP, Dos Santos FB. 30 years of fatal dengue cases in Brazil: a review. BMC Public Health. 2019;19(1):329. https://doi.org/10.1186/s12889-019-6641-4

2. WHO Guidelines Approved by the Guidelines Review Committee. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: World Health Organization; 2009.
3. da Silva NS, Undurraga EA, Verro AT, Nogueira ML. Comparison between the traditional (1997) and revised (2009) WHO classifications of dengue disease: a retrospective study of 30 670 patients. Trop Med Int Health. 2018;23(12):1282-1293. https://doi.org/10.1111/tmi.13155
4. Guzman MG, Harris E. Dengue. Lancet. 2015;385(9966):453-65. https://doi.org/10.1016/S0140-6736(14)60572-9
5. Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. N Engl J Med. 2012;366(15):1423-32. https://doi.org/10.1056/NEJMra1110265
6. de Almeida RR, Paim B, de Oliveira SA, Souza AS Jr, Gomes ACP, Escuissato DL, et al. Dengue Hemorrhagic Fever: A State-of-the-Art Review Focused in Pulmonary Involvement. Lung. 2017;195(4):389-395. https://doi.org/10.1007/s00408-017-0021-6
7. Rodrigues RS, Brum AL, Paes MV, Póvoa TF, Basilio-de-Oliveira CA, Marchiori E, et al. Lung in dengue: computed tomography findings. PLoS One. 2014;9(5):e96313. https://doi.org/10.1371/journal.pone.0096313
8. Brasil. Ministério da Saúde. Secretária de Vigilância à Saúde. Boletim Epidemiológico. Brasília: Ministério da Saúde. 2019 Sep;50(22).
9. Marchiori E, Ferreira JL, Bittencourt CN, de Araújo Neto CA, Zanetti G, Mano CM, et al. Pulmonary hemorrhage syndrome associated with dengue fever, high-resolution computed tomography findings: a case report. Orphanet J Rare Dis. 2009;4:8. https://doi.org/10.1186/1750-1172-4-8
10. Marchiori E, von Ranke F, Zanetti G, Hochhegger B. Dengue hemorrhagic fever: another cause of diffuse alveolar hemorrhage in immunocompetent patients. Respir Med. 2012;106(12):1807-8; author reply 1809. https://doi.org/10.1016/j.rmed.2012.07.014
11. von Ranke F, Zanetti G, Hochhegger B, Marchiori E. Infectious diseases causing diffuse alveolar hemorrhage in immunocompetent patients: a state-of-the-art review. Lung 2013;191(1):9-18. https://doi.org/10.1007/s00408-012-9431-7