CASE REPORT: FALSE-POSITIVE DENGUE NON-STRUCTURAL PROTEIN 1 ANTIGEN IN A PATIENT WITH COVID-19 INFECTION

¹Yohanes Firmansyah, ¹Jessica Elizabeth; ¹Hendsun Hendsun, ²Darren Gosal

¹Faculty of Medicine, Tarumanagara University, Jakarta, Indonesia

²Faculty of Medicine, Atmajaya University, Jakarta, Indonesia

E-mail: yohanesfirmansyah28@gmail.com

Abstract. Early diagnosis of dengue fever and COVID-19 is made very easy due to technological advancements. The non-structural protein 1 antigen test strips are widely used in various regions; however, false-positive events have begun to be reported in the dengue-endemic areas with the COVID-19 pandemic, even though statistically non-structural protein 1 antigens are very specific to dengue infection. We reported a case of the false-positive non-structural protein 1 test in a patient with COVID-19 infection.

Keywords: *Non-Structural Protein 1 (NS1) Antigen; Dengue; COVID-19; False-Positive.*

Problem Statement and Analysis of the Recent Research

In December 2019, an outbreak of pneumonia caused by a new type of coronavirus occurred in Wuhan, Hubei Province, and has spread rapidly throughout the mainland China [1-3]. After the identification and isolation of the virus, the pathogen causing pneumonia has initially been referred to as the 2019 novel coronavirus (2019-nCoV) [4], but later it was officially renamed by the World Health Organization (WHO) as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5]. On January 30, 2020, WHO declared an outbreak of SARS-CoV-2 as a Public Health Emergency of International Concern that should be of particular concern. Compared to SARS-CoV, which caused the SARS outbreak in 2003, SARS-CoV-2 has a more substantial transmission capacity. The rapid increase in confirmed cases made the prevention and control of COVID-19 very serious [6].

Until July 9, 2020, SARS-COV-2 infection accounted for 11,841,326 cases worldwide with a total death of 544,736 people. The areas with the highest SARS-CoV infection are the United States with 6,125,802 cases, Europe with 2,827,789 cases, the Eastern Mediterranean with 1,222,070 cases, Southeastern Asia with 1,032,167 cases, and Africa with 397,942 cases [7]. As part of the Southeast Asian country, Indonesia reported 70,736 cases with a death toll of 3,417 cases on July 9, 2020 [8, 9].

Dengue fever is a systemically transmitted viral disease that can go away on its own. Dengue fever can cause fever, myalgia, rash, leukopenia, and thrombocytopenia [10, 11]. Clinical presentations and laboratory examination of dengue fever can mimic other viral infections, including COVID-19 infection [12-14]. Such conditions have become a serious problem. Indonesia is a region with a long history of dengue fever [15].

Commercial tools for rapid in-vitro diagnosis of dengue infection have been developed and adopted as strong evidence for early laboratory confirmation of the disease in endemic areas [16, 17]. The reported sensitivity of the non-structural protein 1 (NS1) antigen test ranged between 48.5% and 58.6%, and the specificity ranged between 92.5% and 99.4%. The combined sensitivity of NS1 dengue antigen and the immunoglobulin M (IgM) antibody test increased to 89.9-92.9%, with a specificity of 75.0-88.8% [18].

In this case report, we discussed cross-reactivity of the NS1 antigen test in confirmed cases of COVID-19 infection.

Case Presentation

A 24-year-old woman presented with fluctuating fever reaching 39°C. The patient was a medical officer at a hospital in Central Java and had a history of contact with a patient confirmed to be positive for COVID-19.

Fever tended to increase from noon, peaked in the afternoon and lasted for four days. The patient complained of myalgia and sore throat. Complaints of bumps, colds, and shortness of breath were excluded. The patient's blood pressure was 120/80 mmHg with a pulse rate of 80 beats per minute and oxygen saturation of 99%. During auscultation of the heart, no murmurs or irregularities were found; during lung auscultation, no rhonchi and wheezes were found. Other physical examinations were within normal limits. The patient was hospitalized and treated with intravenous maintenance fluids: paracetamol - 3x1 gram, and ceftriaxone - 1x2 gram.

Laboratory tests on the 2nd day after symptom onset were as follows: hemoglobin - 12.2 g/dL, hematocrit - 35.8%, platelets - 210,000/ μ L, erythrocytes - 4.14 million, leukocytes - 3160/ μ L with a lymphocyte count of 23.4%, basophils - 0.0%, neutrophils - 60.8%, monocytes - 15.5%. The neutrophil-to-lymphocyte ratio was 2.6, and the absolute lymphocyte count was 739 cells/mm³. The posteroanterior (PA) chest X-ray taken on the 2nd day after symptom onset and computed tomography (CT) scan of the chest taken on the 4th day after symptom onset showed a normal picture of the heart and lungs without any infiltrates or increased vascularity (Fig. 3). On the 2nd day of fever, the result of the NS1 test was positive.

Oropharyngeal and nasopharyngeal swab samples were taken on the 4th day of symptom manifestation for polymerase chain reaction (PCR) testing for the COVID-19 DNA strain. Special treatment for COVID-19 was planned after obtaining the PCR results.

Fever disappeared on the 4th day after symptom onset. However, sore throat and myalgia persisted until the 7th day after symptom onset. On the 7th day, the following symptoms appeared: erythematous colored skin lesions of lenticular size distributed symmetrically in the upper and lower limb regions, multiple notably discrete maculopapular rashes, and itching sensation (Fig. 1, 2). The lesions did not appear in any region of the body and were more pronounced on the 8th-9th days after symptom onset. The patient was given oral loratadine - 3x10 mg and Nerilon cream for her skin lesions. The skin lesions

Fig. 1. Outline of symptoms experienced by patient

disappeared by the 10th day after symptom onset.

On the 9th day after symptom onset, the PCR test results were found to be positive for COVID-19. According to the Recommendations of the Indonesian Medical Association for mild symptoms, the patient was given the following treatment regimen: azithromycin - 1x500 mg for three days, chloroquine phosphate - 2x500 mg for five days, oseltamivir - 2x75 mg for five days, 3x1 vitamin C tablets, and an asymptomatic drug in the form of 1x30 mg lansoprazole to be taken with azithromycin.

Discussion

COVID-19 infection in areas where dengue virus is endemic should be of particular concern. Gabriel Yan et al. reported 2 cases of COVID-19 patients coinfecting with dengue fever in Singapore. These cases shared similar clinical course of the disease. They both cases tested negative for dengue using a rapid test, then, they were discharged and returned to the hospital for persistent fever and diagnosed with dengue fever and SARS-CoV-2 coinfection [19]. Joob et al. also reported a patient coinfecting with SARS-CoV-2 and dengue virus in Thailand. The patient first developed a petechial rash and was diagnosed with dengue fever. However, the patient further developed more respiratory symptoms and was re-diagnosed with COVID-19 infection. These cases raised concern that patients with fever can get infected with SARS-CoV-2 and

dengue simultaneously in dengue-endemic areas such as Singapore, Thailand, and Malaysia in Southeast Asia and Brazil in South America [20]. According to a recent study of 1,099 patients conducted by Guan et al., 87.9% of COVID-19 patients had a fever, 67.7% of patients had cough, and 13.7% of patients had headache. Some patients only experienced fever when infected with SARS-CoV-2 [21]. In another study of 1,792 patients, 100% of patients had dengue fever, and 25.7% of patients had headache [22].

COVID-19 patients can show the same clinical signs as dengue patients. Furthermore, the cases in Singapore were misdiagnosed and later confirmed with COVID-19 [19] that indicated that misdiagnosis of patients with atypical symptoms is possible. Therefore, steps should be taken to differentiate patients with fever and headache from dengue fever and COVID-19; these atypical symptoms should be of major concern, especially in developing countries with a high incidence of dengue fever, as in Southeast Asia and South America [23].

False-negative NS1 tests were reported in dengue serotypes 2 and 4 infections [24, 25]. NS1 tests were also reported to be less sensitive in secondary dengue [16, 26, 27]. A little is known about the cause of false-positive NS1 test, except for possible -cross-reactivity with other flaviviruses and possibly with cytomegalovirus (CMV) [28, 29].

Two prospective studies identified false-positive NS1 in

Fig. 2. Skin manifestations on the 4th day

Fig. 3. Patient's thorax x-ray on the 2nd day

patients with febrile illness evaluated with the NS1 test using the SD Bioline Dengue Duo kit in Cambodia and the NS1 antigen enzyme-linked immunosorbent assay (ELISA; Platelia; Bio-Rad Laboratories) in Vietnam [16, 30]. False-positive dengue NS1 tests have not been reported in hematological malignancies. Although there are case reports of dengue fever causing hemophagocytosis [31, 32].

Conclusions

The rapid test and PCR test of nasopharyngeal swabs carrying out in severe suspicion of COVID-19 help us a lot. Furthermore, dengue NS1, IgM, and IgG tests should be used to differentiate between these two infections with atypical symptoms in countries where dengue virus is endemic.

Although the NS1 test is specific to dengue infection, we reported a case of the false-positive NS1 test in a patient with COVID-19 infection. We are very concerned that the rapid test, the PCR test, the NS1 test, IgM, and the dengue IgG test were performed on the patients with a high suspicion of being infected with a second virus.

Consent for Publication

Not Applicable

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declared that they have no conflicts of interest.

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Conflict of Interest

The authors declared that they have no conflicts of interest.

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