International Journal of Infectious Diseases 102 (2021) 152–154

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Serological cross-reaction and coinfection of dengue and COVID-19 in Asia: Experience from Indonesia

Sri Masyeni[a,b], Marsha S. Santoso[c], Putu Dyah Widyaningsih[a,b], DG Wedha Asmara[a,b], Firzan Nainu[d], Harapan Harapan[e,e,f,g,h,**], R Tedjo Sasmono[c,*]

[a] Department of Internal Medicine, Faculty of Medicine and Health Sciences Universitas Warmadewa, Denpasar, Bali 80235, Indonesia
[b] Department of Internal Medicine, Sanjiwani Hospital, Denpasar, Bali 80235, Indonesia
[c] Eijkman Institute for Molecular Biology, Jakarta 10430, Indonesia
[d] Faculty of Pharmacy, Hasanuddin University, Makassar 90245, Indonesia
[e] Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia
[f] Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia
[g] Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia
[h] Infectious Disease Laboratory, Universitas Syiah Kuala, Banda Aceh, 23111, Indonesia

ARTICLE INFO

Article history:
Received 8 September 2020
Received in revised form 11 October 2020
Accepted 22 October 2020

Keywords:
Dengue
Co-Infection
Mixed-Infection
Cross-Reactivity
Misdiagnosis
COVID-19

ABSTRACT

Similar symptoms and laboratory findings between dengue and coronavirus disease 2019 (COVID-19) pose a diagnostic challenge in some dengue-endemic countries in Asia. In this study, we reported three cases of suspected COVID-19-dengue coinfection in hospitals of Bali, Indonesia. Serological data demonstrated that patients with positive results for dengue virus (DENV) NS1 antigen and anti-dengue IgM were also reactive to COVID-19 rapid antibody tests, suggesting dengue–COVID-19 coinfection. However, two patients were later confirmed negative for SARS–COV-2 by qRT-PCR, implying a plausible cross-reactivity of anti-dengue and anti–COVID-19 antibodies in the serological test. Coinfection of dengue and COVID-19 was evident in one patient, following confirmation of SARS–COV-2 by qRT-PCR and DENV infection using the NS1 antigen serology test. This case was the first case of dengue and COVID-19 coinfection in Indonesia and revealed possible cross-reactivity between SARS–COV-2 and DENV antibodies based on rapid serological tests. Our study indicates a public health concern regarding COVID-19 and dengue detection in Indonesia as well as in other dengue-endemic countries, and it is important for these nations to manage both pathogens concurrently.

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has now spread to most countries around the world, resulting in a global pandemic (Harapan et al., 2020a). SARS-CoV-2 is primarily transmitted from person-to-person through droplets while coughing and sneezing, from symptomatic and pre-symptomatic patients and probably from asymptomatic individuals as well (Bai et al., 2020). Although there is yet no specific medication for treating COVID-19, multiple medicines are being assessed in clinical trials (Frediansyah et al., 2020).

The pandemic is still ongoing in Asian countries in which dengue, caused by dengue virus (DENV), has been endemic for decades. Some countries in the region are facing dengue outbreaks amid the COVID-19 pandemic creating a double-burden on resources and health systems (Harapan et al., 2020b). In addition, with similar clinical symptoms for both diseases, this creates a critical problem of misdiagnosis and the possibility of double infection occurring within the same individual at the same time.

Rapid tests are useful for easy, convenient, and fast diagnosis, particularly in areas where diagnostic capabilities are limited. Numerous rapid tests for the detection of COVID-19 antibodies were commercially available and widely used soon after the COVID-9 pandemic began, while dengue antigen/antibody rapid tests have been available for years. However, the accuracy of these

* Corresponding author at: Eijkman Institute for Molecular Biology, Jl. Diponegoro 69, Jakarta 10430, Indonesia.
** Corresponding author at: Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Jl. T. Tanoeh Abe, Darussalam, Banda Aceh 23111, Indonesia.
E-mail addresses: masyeniputu@yahoo.com (S. Masyeni), marshasantoso@eijkman.go.id (M.S. Santoso), dr.putudyah@gmail.com (P.D. Widyaningsih), on.wedha@gmail.com (D.W. Asmara), firzannainu@unhas.ac.id (F. Nainu), harapan@unsyiah.ac.id (H. Harapan), sasmono@eijkman.go.id (R.T. Sasmono).

https://doi.org/10.1016/j.ijid.2020.10.043

tests vary and are influenced by the day in the disease progression that the test is performed (Blacksell et al., 2011; Deeks et al., 2020). Confirmatory testing for both COVID-19 and dengue is through nucleic acid amplification tests using polymerase chain reaction (PCR) tests. However, these often require referral to more advanced facilities, adding time to the yield of results. Altogether, these have consequences for both patient care and public health, particularly in diagnosing the COVID-19 cases in low-resource countries in Asia. In this case series, we outlined and compared three cases of suspected COVID-19-dengue mixed infection based on clinical presentation and raised the concern of cross-reactivity of SARS-CoV-2 and DENV based on rapid serology tests in Indonesia.

Case presentation

Three cases of suspected COVID-19-dengue coinfection were reported in Kasih Ibu Hospital and Sanjiwani Hospital in Denpasar, Bali, Indonesia. The first case was a 24-year-old woman presenting with a 2-day onset of high and continuous fever, as well as myalgia, headache, arthralgia, retro-orbital pain, nausea, and vomiting. She did not report cough, sore throat, or shortness of breath. Other vitals were normal upon admission, and initial blood work showed leukopenia (2380/μL), thrombocyte count of 124,000/μL, and slightly elevated levels of aspartate aminotransferase (AST, 45 U/L) and alanine transaminase (ALT, 57 U/L). Dengue rapid tests, such as Standard Q Dengue Duo (SD Biosensor, Korea), were positive for NS1 antigen and anti-dengue IgM and negative for anti-dengue IgG. COVID-19 IgG rapid test was also reactive with two different kits, manufactured by Vazyme Biotech (Nanjing, China) and Wondfo Biotech (Guangzhou, China). Simultaneous detection and serotyping using abTES DEN/CHIKU 5 qPCR qRT-PCR (AIT Biotech, Singapore) showed DENV-2 infection, while RT-PCR for SARS-CoV-2 using Liferiver Novel Coronavirus (2019-nCoV) Real Time Multiplex RT-PCR Kit (BioVendor, Czech Republic) of nasopharyngeal swab was negative. Other laboratory parameters and radiology tests, including chest X-ray, were normal. Follow-up blood work showed decreasing leucocyte (1970/μL) and platelet counts (108,000/μL), but there were no signs of plasma leakage, bleeding, shock, or other complications. The patient was diagnosed with dengue fever and survived.

The second case was a 59-year-old woman with a 5-day high and continuous fever, dry cough, sore throat, myalgia, headache, arthralgia, and nausea, without any shortness of breath or any comorbidities. She arrived in Bali after a three-week-holiday in Thailand. Vital signs were normal upon admission, and initial blood work showed leukopenia (1020/μL), thrombocyte count was 141,000/μL, and elevated levels of AST (87 U/L). Dengue rapid tests were positive for NS1 and anti-dengue IgM, while negative for anti-dengue IgG. qRT-PCR test revealed DENV-3 infection. COVID-19 rapid test was also reactive, but qRT-PCR for SARS-CoV-2 of nasopharyngeal swab was negative. Chest X-ray showed bronchitis. On the second day of hospitalization, the patient was hypotensive and had to undergo fluid resuscitation, and the platelet count dropped to 82,000/μL. The vitals stabilized by the next day, and platelet count rose to 118,000/μL and 141,000/μL over the next two days. The patient was diagnosed with grade III dengue hemorrhagic fever (DHF).

The last patient was a 69-year-old woman with a fever of one-week-onset, myalgia, arthralgia, nausea, and mild cough. She reported no other symptoms. Upon admission, vitals were normal with a body temperature of 37.8 °C. Other physical examinations were normal. She had Parkinson's disease and was regularly taking 100 mg of levodopa and 25 mg of benserazide. On the day of admission, she was tested positive using a dengue NS1 antigen rapid test, namely Panbio NS1 Dengue Early Rapid (Brisbane, Australia), and was diagnosed with dengue fever. Subsequent qRT-PCR analysis of the nasopharyngeal swab of the corresponding patient confirmed her as SARS-CoV-2-positive despite the fact that chest X-ray was normal. Serotyping qRT-PCR test on serum sample collected on day 7 of admission came with undetected DENV, and repeated dengue rapid test using Standard Q Dengue Duo (SD Biosensor, Korea) was positive for NS1 and both anti-dengue IgM and IgG. Other laboratory results showed mild hyponatremia (130 mmol/L), leukopenia (3400/μL), monocytosis (9%), low eosinophil level (0%), and elevated erythrocyte sedimentation rate (ESR) at 42 mm/h. Platelet counts and hematocrit levels were normal, amounting to 236,000/μL and 43.2%, respectively. CD4 level was also normal. The patient lives at home with her husband and daughter. The patient and her husband were not involved in any employment/work and spent most of their time at home. However, their daughter regularly left home to work and shop for groceries at the market. A follow-up test revealed that the daughter's husband was positive for SARS-CoV-2, while she was, surprisingly, negative.

Discussion

In dengue-endemic regions such as in Asia, misdiagnosis between COVID-19 and dengue can be highly problematic and could affect management of these diseases. This is mainly because approximately 80% of COVID-19 cases are mild to moderate cases with unspecific symptoms and mimic dengue (Henrina et al., 2020). Apart from fever, which is the chief complaint of most cases of dengue and COVID-19, skin manifestations including rash or petechiae, which are commonly found in dengue, have also been commonly reported in COVID-19 (Criado et al., 2020), and thus, the challenge of discriminating one from another is increased.

One of the easiest, most convenient, and fastest point-of-care testing to diagnose dengue and COVID-19 is by rapid serology tests. However, cross-reactivity between COVID-19 and dengue has been reported in Singapore (Yan et al., 2020), Thailand (Prasitsirikul et al., 2020), and Indonesia (Kembuan, 2020), where dengue antibodies were detected in confirmed COVID-19 patients (i.e. false-positive dengue serology among COVID-19 patients). Our data also suggested the possible cross-reactivity between DENV and SARS-CoV-2 which led to false-positive COVID-19 serology among dengue patients. This was also reported previously in Italy where 1 out of 44 DENV-positive sera resulted in a false-positive result for COVID-19 antibodies (Spinicci et al., 2020). Our study also emphasizes the possibility of coinfection of DENV and SARS-CoV-2 in dengue-endemic countries in Asia that might require special management strategies in clinical settings.

A recent study found that a false-positive result could occur for both COVID-19 serology among dengue patients and, reciprocally, dengue serology among COVID-19 patients (Lustig et al., 2020). The cross-reactivity between SARS-CoV-2 and DENVs when using a rapid serology test will be a significant hurdle to rely on the laboratory diagnosis of COVID-19 (as well as dengue) based on the use of rapid serology tests, particularly in the early phase of infection. A systematic review of 15,976 samples revealed the inadequacy of pooled results for IgG, IgM, IgA, total antibodies, and IgG/IgM (using a combination of ELISA, chemiluminescence immunoassays, and lateral flow assays). While the sensitivities of all approaches were less than 30.1% during the first week of onset of symptoms (Deeks et al., 2020), the numbers were improved in the second week and reached the highest in the third week; 72.2% (day 8–14), 91.4% (15–20 days), and 96.0% (21–35 days) for IgM/IgG combination (Deeks et al., 2020). This indicates that the use of antibody tests, in particular rapid test employing lateral flow immunoassays, have limited benefits in the point-of-care testing.

Mixed infection of dengue and COVID-19 requires special attention from all dengue-endemic countries in Asia, especially the

ones with limited resources. To our knowledge, this is the first confirmed case of coinfection of dengue and COVID-19 in Indonesia. Two clear cases of coinfection were reported previously in Reunion Island (Verduyn et al., 2020) and in Mayotte (Epelboin et al., 2020) in France. Nevertheless, possible coinfection was also observed in Asia (Miah and Husna, 2020). A study in Bangladesh found that coinfection occurred among 4 out of 20 patients, and coinfection was associated with a high mortality rate (Saddique et al., 2020), alarming the dengue-endemic countries in the region. Therefore, maintaining dengue-preventive measures, including enhancing vector control measurers amid the COVID-19 pandemic, is urgently needed. In addition, establishing more laboratory testing facilities that can conduct PCR testing is critical.

Conclusion

Our study provided evidence of cross-reactivity between DENV and SARS-CoV-2, which lead to false-positive COVID-19 serology among dengue patients. This underscores the importance of a simple and affordable rapid test that is capable of differentiating between DENV and SARS-CoV-2 with high sensitivity in the early phase of infection as well as enhancing the laboratory network capacities in the region. In addition, healthcare workers in dengue-endemic countries across the Asian continent should be aware of coinfection of DENV and SARS-CoV-2 and its dangerous impact on patient mortality rate. Refining the existing guidelines to accommodate the differentiation of both infectious diseases (and their pathogenic causality) is of the utmost importance. Follow-up studies are needed to evaluate the outcome of dengue and COVID-19 coinfection in the Asian regions.

Conflict of interest

The authors declare no conflicts of interest.

Funding

This work is partly funded by ASTRA International Tbk to RTS.

Ethical approval

Written informed consent for publication was sought from each patient.

Acknowledgement

We would like to thank patients and medical staff involved in this study.

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