SARS-CoV-2 and Dengue virus Co-infection. A Case Report

Marcelo Victor Radisic[1,2], Maria Ayelén Piro[1], Ignacio Mori[1], Flavio Rotryng[1], Joaquín Francisco Santamarina[1]

[1]Sanatorio Finochietto, Ciudad Autónoma de Buenos Aires, Argentina;
[2]Instituto de Trasplantes y Alta Complejidad, Ciudad Autónoma de Buenos Aires, Argentina

SUMMARY

Coinfection of SARS-CoV-2 and dengue virus has not been previously reported. We report a confirmed case with favourable outcome, but whether the occurrence of simultaneous infections may alter the usual clinical course of each infection is still unknown.

Keywords: SARS-CoV-2, dengue, coinfection.

INTRODUCTION

Clinical and laboratory manifestations of COVID-19 and dengue present a considerable overlap [1, 2]. Fever, myalgias, malaise, diarrhea and dermatological manifestations may occur in both, making it impossible to differentiate these viral infections on clinical grounds.

In COVID-19, the most common hematological abnormality is lymphopenia, present in about 80% of the cases. However, leukocyte count is usually normal, but leukopenia as well as mild thrombocytopenia may be observed in 30% of patients. These haematological abnormalities are more prominent among severe vs non-severe cases [3].

Liver function tests are also altered, with elevations of alanine aminotransferase (25%) and aspartate aminotransferase (33%). Acute phase reactants, as serum C reactive protein (increased in >60% of patients), are also frequently abnormal [4].

In dengue cases, leukopenia and thrombocytopenia are more frequent than in COVID-19 infection, being observed in about 70-80% of patients [5]. However, laboratory abnormalities are not useful for differential diagnosis between dengue and COVID-19, as they may be present (with variable frequencies and severity) in both viral infections.

COVID-19 cases have been erroneously diagnosed as dengue in the context of a local dengue outbreak. In one case, initial manifestation of COVID-19 was a petechial rash with thrombocytopenia, and in the context of high local incidence of dengue, the patient was considered as a dengue case. Only after the later development of respiratory manifestations the patient was studied and diagnosed as a COVID-19 case [6].

The possibility of misdiagnosis may be aggravated by the occurrence of false positive serological tests for dengue in the COVID-19 infection setting [7].

The widespread dissemination of COVID-19 pandemic was destined to overlap with the activity of other widely prevalent infectious diseases. In countries with current high dengue activity, the eventual challenge of managing dual outbreaks has been anticipated [8, 9].

However, clinical cases of COVID-19 and dengue coinfection have not been yet described. In Argentina there is an ongoing outbreak of dengue and we were able to diagnose such a case of coinfection [10].

Corresponding author
Marcelo Victor Radisic
E-mail: marceloradisic@gmail.com

CASE REPORT

The patient was a 25-year-old male. He was admitted on April 14th. He started 48 hours before his admission with asthenia, headache, joint and muscle pain. The day of admission, he added fever and sore throat, without any other symptoms. Medical history was negative. He denied mosquito bites and contact with cases suspicious or confirmed of COVID-19 infection and was observing quarantine. He lives in Buenos Aires, Argentina.
On admission, heart rate was 112 per minute (pm), respiratory rate 20 pm, O_2 Sat 98% (room air). Temperature 38°C. Physical examination was unremarkable. Chest x-ray showed a doubtful right lower lobe infiltrate, and on April 17th a chest-CT scan was performed, with no pathological images in the lungs. Mild splenomegaly was observed (Figure 1). As there was an ongoing dengue and

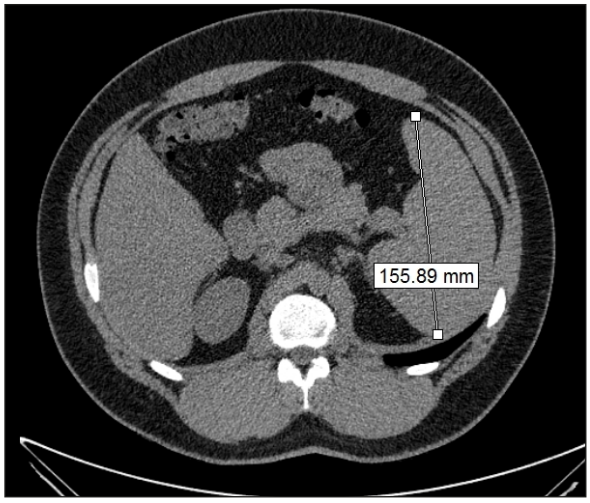

Figure 1 - Abdominal CT scan showing enlarged spleen in a patient with SARS-CoV-2 and dengue virus coinfection.

Table 1 - Laboratory findings in a case of SARS-CoV-2 and dengue virus coinfection.

	April 14th	*April 15th*	*April 16th*	*April 17th*	*April 21st*
RBC count [x10⁶][/mm³]	5.79		5.94	5.60	5.74
Hematocrit [%]	48		50	47	48
Hemoglobin [g/dL]	16.1		16.8	15.5	16
WBC count /mm³	5,002		4,165	3,158	4,238
Lymphocytes %	14		34	27	38
Neutrophiles %	64		49	58	46
C- Reactive Protein mg%			10.8		
ERS [mm/1st hour]			3		
D-dimer [ng/mL]					430
Ferritine [ng/mL]			444		1,200
Platelet count [/mm³]	126,200		108,000	101,200	108,100
Total Bilirubin [mg/dL]	1.13		0.96	0.89	
ALT [IU/L]	60		58	51	
AST [IU/L]	36		65	85	
Alk P [IU/L]	196		185	168	
LDH [IU/L]			270		507
Albumin [g/L]			4.4	4.2	
Urea [mg/dL]	23		26	27	
Creatinine [mg/dL]	1.2		1.34	1.14	
IgM dengue CO		11.1 COI [positive]			
NS1 dengue COI		139.91 [positive]			
PCR SARS-CoV-2	POSITIVE				

RBC: Red Blood Count; WBC: White cells Blood Count; ERS: Erythrocyte Sedimentation Rate; ALT: Alanine Transaminase; AST: Aspartate Transaminase; Alk P: Alkaline Phosphatase; LDH: Lactic Dehydrogenase; COI: Cut-off Index.

COVID-19 epidemic, the patient was tested for both viruses. NS1 specific dengue antigen (STANDARD Q Dengue NS1 Ag, SD Biosensor, Republic of Korea) was positive in a blood sample and a nasopharyngeal swab was positive for SARS-CoV-2 real time-PCR (Bosphore Novel Coronavirus [2019-nCoV] Detection Kit, Anatolia Diagnostics and Biotechnology Products Inc., Turkey).
The patient turned afebrile on April 19th and was discharged on April 21th. He was followed-up by telephone and remained healthy without clinical symptoms at the last follow-up on May 15th. Laboratory data is provided in Table 1.

DISCUSSION

Coinfection of COVID-19 and other microorganisms such as *Mycoplasma pneumoniae,* influenza virus, cytomegalovirus, HIV, *Legionella, Pneumocystis jirovecii,* and even coinfection with multiple respiratory viruses have been reported [11-17].
Patients with COVID-19 and influenza virus coinfection did not appear to show a more severe condition and they showed similar clinical characteristics as those patients with COVID-19 infection only [12].
However, whether the clinical course of simultaneous infection with other pathogens may be altered by the immunologic dysregulation that is frequently present in SARS-CoV-2 infections is yet unknown, and a deleterious interaction in the case of co-infection with SARS-CoV-2 and dengue seems a logical concern.
Normal immune response to dengue has not yet been well characterized. The main
innate immune response is type I IFN [13]. Patients with severe clinical manifestations [severe dengue] had a more intense pro-inflammatory cytokine response. IL-1β, IFN-γ, IL-4, IL-6, IL-13, IL-7 and GM-CSF are significantly increased in patients with severe dengue when compared to mild disease forms. After the normal initial, transient elevation of IL-6 observed in dengue infections, raising levels at the time of a shock state have been reported, suggesting that IL-6 levels may correlate with the severity of the illness [14].
Antibody-dependent enhancement [ADE] of viral infection is another mechanism that may underlie development of severe dengue disease [15].
Similarly, a marked inflammatory dysregulation seems to be involved in the pathogenesis of severe COVID-19 disease. Higher serum levels of proinflammatory cytokines [TNF-α, IL-1, and IL-6] and chemokines were found in patients with severe COVID-19 compared with individuals with mild disease [16]. I has been speculated that ADE is also a possible underlying mechanism for severe COVID-19. Early, sub-optimal antibody activity cannot completely clear the virus, but instead leads to persistent viral replication and inflammation [17]. Hypothetically, amplification of a dysregulated, inappropriate immune response in the case of coinfection with dengue virus and SARS-CoV-2 may occur.
Opportunistic infections in patients with COVID-19 [and not known immunodeficiencies] have been reported [10, 13]. These infections may have been facilitated by lymphocytopenia, a common finding in patients with severe SARS-CoV-2 infection [18]. This negative immune regulation may also be a mechanism hampering immune response to dengue virus infection [19].
In the present case, interaction between SARS-CoV2 and dengue infection leading to an unwanted outcome was not observed. However, clinicians should be aware of the possibility of coinfections in areas with overlapping outbreaks, and for the potential of a deleterious interplay between these viruses.

Acknowledgments
To Brenda Koliren and Silvia Lang, from MEC Translations & Training, for their assistance in preparing the English manuscript.
To the courageous Internal Medicine team of our institution and all healthcare workers fighting SARS-Cov2 pandemic around the world.

Conflict of interest
None.

Funding
None.

Ethical aspects
Written consent was obtained from the patient. Copy of the document is available on request.

REFERENCES

[1] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel

coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020; 395 (10223), 507-13.
[2] Yan G, Pang L, Cook AR, et al. Distinguishing Zika and dengue viruses through simple clinical assessment, Singapore. *Emerg Infect Dis.* 2018; 24 (8), 1565-8.
[3] Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. *Am J Hematol*. 2020; 95 (7), 834-47.
[4] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020; doi:10.1001/jama.2020.12839
[5] Oliveira ÉCLD, Pontes ERJC, Cunha RVD, Fróes ÍB, Nascimento DD. Alterações hematológicas em pacientes com dengue. *Rev Soc Bras Med Trop.* 2009; doi:10.1590/s0037-86822009000600014
[6] Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. *J Am Acad Dermatol.* 2020; 82 (5), e177.
[7] Yan G, Lee CK, Lam LTM, et al. Covert COVID-19 and false-positive dengue serology in Singapore. *Lancet Infect Dis*. 2020; 20 (5), 536.
[8] Lorenz C, Azevedo TS, Chiaravalloti-Neto F. COVID-19 and dengue fever: A dangerous combination for the health system in Brazil. *Travel Med Infect Dis.* 2020; 35, 101659.
[9] Wu D, Lu J, Liu Q, Ma X, He W. To alert coinfection of COVID-19 and dengue virus in developing countries in the dengue-endemic area. *Infect Control Hosp Epidemiol*. 2020; 1. doi:10.1017/ice.2020.187
[10] Boletín Epidemiológico Semanal [BES]. Ciudad Autonoma de Buenos Aires. n°192, Año V/24 de abril 2020. Gerencia Operativa de Epidemiologia. SSPLSAN. MINISTERIO DE SALUD DE LA CABA https://www.buenosaires.gob.ar/sites/gcaba/files/bes_192_se_15_vf.pdf Accesed April 27th, 2020
[11] Fan BE, Lim KGE, Chong VCL, Chan SSW, Ong KH, Kuperan P. COVID-19 and mycoplasma pneumoniae coinfection. *Am J Hematol.* 2020; 95 (6), 723-4.
[12] Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. *J Med Virol.* 2020; doi:10.1002/jmv.25781
[13] Uno N, Ross TM. Dengue virus and the host innate immune response. *Emerg Microbes Infec.* 2018; 7 (1), 167.
[14] Butthep P, Chunhakan S, Yoksan S, Tangnararatchakit K, Chuansumrit A. Alteration of cytokines and chemokines during febrile episodes associated with endothelial cell damage and plasma leakage in dengue hemorrhagic fever. *Pediatr Infect Dis J.* 2012; 31 (12), e232-8.
[15] Pang T, Cardosa MJ, Guzman MG. Of cascades and perfect storms: the immunopathogenesis of dengue haemorrhagic fever-dengue shock syndrome [DHF/DSS]. *Immunol Cell Biol.* 2007; 85 (1), 43-5.
[16] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020; doi: 10.1093/cid/ciaa248.
[17] Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-Mediated Inflammatory Responses: from mechanisms to potential therapeutic tools. *Virol Sin.* 2020; 35 (3), 266-71.
[18] Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020; 382 (18), 1708-20.
[19] Ng KH, Zhang SL, Tan HC, et al. Persistent Dengue infection in an immunosuppressed patient reveals the roles of humoral and cellular immune responses in virus clearance. *Cell Host Microbe*. 2019; 26 (5), 601-5.