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COVID-19 (Symptomatic Non-Respiratory) with Type 2 Diabetes Mellitus

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ABSTRACT

COVID-19 is a respiratory infection caused by a new strain of Coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is highly contagious, primarily through respiratory droplets and contact. Typical symptoms include fever, cough, and shortness of breath. Weakness, nausea, and vomiting are often accompanied by respiratory symptoms but are sometimes confusing when these symptoms occur without respiratory symptoms. COVID-19 can affect any age group, are more common in adults and males and increase in patients with comorbidities. One of the most common comorbidities is Diabetes Mellitus (DM). A 40-year-old male patient complained of fever and weakness for three days. Nausea and vomiting since nine days before hospital admission, accompanied by painful swallowing, heartburn, and decreased appetite. History of going out of town and eating with friends 14 days before access to the hospital. Laboratory examination results: 6600 leukocytes/mm^3, 264,000/mm^3 platelets, NLR 2.3, 209 mg/dL of blood glucose, HbA1C 8.6%, SGOT 67 IU/L, SGPT 102 IU/L, IgG SARS-CoV-2 reactive, positive TCM SARS-CoV-2 (N2 Ct 18 and E Ct 20.3), and the duration of negative conversion of RT-PCR SARS-CoV-2 results was 19 days. The SARS-CoV-2 virus not only infects pneumocytes but also gastrointestinal, pancreatic, and endothelial cells via ACE2 receptors in DM patients, causing increased cell wall permeability to foreign pathogens and viral replication in the gastrointestinal lining cells. Subsequent enterocyte invasion causes malabsorption resulting in enteric symptoms. Uncontrolled glycemia conditions can slow viral shedding, so the length of negative conversion of RT-PCR SARS-CoV-2 results is prolonged. Based on the data above, the diagnosis in this patient was COVID-19 (symptomatic non-respiratory) with type 2 DM.

Keywords: COVID-19, SARS-CoV-2, diabetes mellitus, male

INTRODUCTION

The coexistence of Coronavirus Disease 2019 (COVID-19) and Diabetes Mellitus (DM) are two diseases that aggravate the other, where DM is related to a bad prognosis of COVID-19 and COVID-19 will cause the dysglycemia condition to worsen in DM patients, exceeding hyperglycemic stress.[1]

COVID-19 is a global epidemic with high mortality and morbidity.[2] This disease causes a respiratory infection caused by a new strain of Coronavirus that is highly infectious, primarily through respiratory droplets and both direct or indirect contact, that is called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee of Taxonomy of Viruses (ICTV).[3,4] This virus was first found in China in December 2019 and is suspected to be a zoonic virus that has mutated or adapted and become pathogenic that spreads globally and rapidly from human to human, causing WHO to state it as a pandemic on March 11th 2020.[5]

COVID-19 infection is affected by the virus virulence factor and the strength of the host's immune system. A virus virulency is affected by the type of virus, mutation, and viral load. While the host's immunity is affected by genetics, elderly age, gender, nutritional status, neuroendocrine-immune regulation, physical status, and whether or not there are any comorbidities.[6]

Diabetes mellitus is one of the most common comorbidities in infectious diseases.[7] Inflammation process linked to DM and chronic hyperglycemia in the blood can cause an inadequate immune response that can worsen infection in patients with DM. Historically, the Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) epidemic are linked with higher severity and mortality in patients with DM. Several studies show that patients with DM have a higher risk of severity when infected with COVID-19 and have

higher mortality than those without DM. A meta-analytical study reported that the prevalence of DM in people infected with SARS-CoV-2 was 10.3% in China, 58% in the USA, and 36% in Italy, while the surveillance from Italy showed a mortality of 34% of COVID-19 patients with DM.[8]

This case report's purpose is to provide information on COVID-19 disease, which doesn't always manifest in the respiratory system but can also manifest clinically in the gastrointestinal system. This phenomenon must be something to be aware of to prevent late diagnosis in COVID-19 patients.

CASE

A 40-year-old male was admitted to Labuang Baji Hospital, Makassar's emergency room, on June 8th, 2020, with a fever and non-respiratory symptoms. The patient was admitted with a chief complaint of fever and full-body weakness three days before admittance. The patient experienced nausea and vomiting nine days before admittance. These symptoms were accompanied by difficulty swallowing, heartburn, and a decrease in appetite. He had a history of traveling during the Ied holidays in the past 14 days. He also had a history of dining with work colleagues two weeks before admittance. The patient has consumed 3x500 mg of Paracetamol and Domperidone for the vomiting. Bowel movements and urinating were within normal limits.

The patient was aware and had vital signs: blood pressure 110/70 mmHg, heart rate 88x/minute, Respiratory rate 20x/minute, temperature 36.7^{0}C. Thorax examination found vesicular breathing on both planes of the lungs.

Laboratory examination showed increased transaminase enzyme, random blood glucose, and HbA1c. Rapid IgG SARS-CoV-2 reactive, and TCM SARS-CoV-2 positive (Figure 1). The patient was confirmed with COVID-19 and typed 2 DM. All laboratory examinations are presented in Table 1.

Table 1. Laboratory examination results (emergency room, June 8th, 2020)

Parameter	Results	Interpretation	Reference Range
Complete blood count			
Hemoglobin	**17.0**	↑	12-16 g/dL
Hematocrit	48.9	N	35-47 %
Leukocyte	6600	N	4400-11300/mm^3
Thrombocyte	264000	N	150000-450000/mm^3
Erythrocyte	**6.39**	↑	3.6-5.8 million/µL
MCV	**76.5**	↓	80-100 fL
MCH	26.6	N	26-34 pg
MCHC	34.6	N	32-36%
Leucocyte count			
Basophil	-	-	0-1 %
Eosinophil	**-**	-	1-6 %
Neutrophil	66.6	N	50-70 %
Lymphocyte	30.3	N	20-40 %
Monocyte	-	-	2-8 %
Clinical chemistry			
Albumin	4.87	N	3.5 – 5.0 g/dL
AST (SGOT)	**67**	↑	10-40 U/L
ALT (SGPT)	**102**	↑	10-55 U/L
GDS	**209**	↑	71-140 mg/dL
HbA1C	**8.6**	↑	3-6.5 %
Urea	15	N	13 – 43 mg/dL
Creatinine	0.7	N	0.6 – 1.4 mg/dL
Uric acid	4.6	N	3.6-8.5 mg/dL
Cholesterol	193	N	< 200 mg/dL
HDL	27	↓	40-60 mg/dL
LDL	142	↑	< 130 mg/dL
Triglyceride	228	↑	< 150 mg/dL
Rapid SARS CoV-2			
Ig-M SARS CoV-2	Negative		Negative
Ig-G SARS CoV-2	Positive		Negative

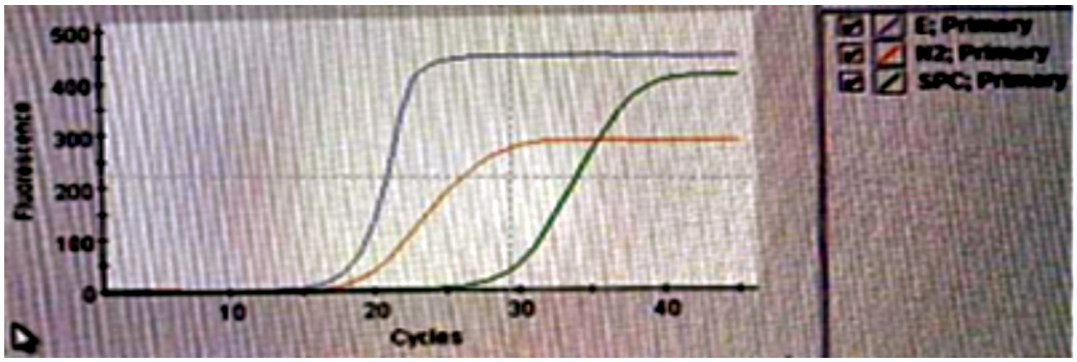
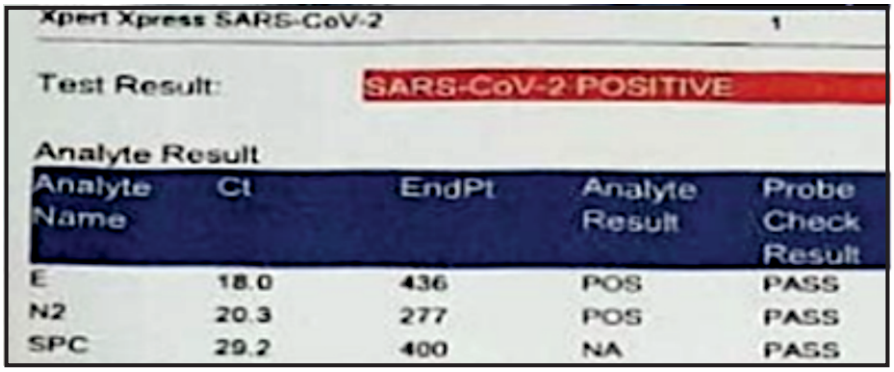


Figure 1. Fluorescent curve graph of SARS-CoV-2 TCM to see the sigmoid curve towards the control (SPC) and both target genes (E and N2)



Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
E	18.0	436	POS	PASS
N2	20.3	277	POS	PASS
SPC	29.2	400	NA	PASS

Figure 2. TCM SARS-CoV-2 results with GeneXpert (gene E detected with a Ct of 20.3, and Gene N2 detected with a Ct of 18

Chest X-ray and electrocardiography (ECG) show normal results. The patient's diagnosis was confirmed as COVID-19 with type 2 DM. The patient was given a Ringer Lactate infusion of 20 drops per minute, Omeprazole injection, and Ondansetron. Oral therapy consisted of 500 mg of Azithromycin, 75 mg of Oseltamivir, vitamin C, 500 mg of Metformin, Proliver, Fibrolivit, and Lantus 0–0–10 units.

DISCUSSION

A male patient with a chief complaint of fever, general body weakness, nausea, vomiting, and heartburn. History of going out of town and dining with friends 14 days before admission. Rapid antibody IgG SARS-CoV-2 test reactive and positive TCM SARS-CoV-2. Other laboratory results had the patient diagnosed as confirmed COVID-19 and type 2 DM (Figure 2 and Table 2).

There are various COVID-19 symptoms, varying from asymptomatic, mild respiratory symptoms to fulminant pneumonia with severe acute respiratory symptoms, septic shock, uncorrected metabolic acidosis, coagulation dysfunction, bleeding, and multiple organ failure with fatal results.[9,10] Most patients infected with SARS-CoV-2 show fever, cough, myalgia, fatigue, and shortness of breath. Other than respiratory symptoms, COVID-19 patients also show gastrointestinal symptoms like diarrhea, nausea and vomiting, anosmia, and ageusia.[10-12]

This case showed gastrointestinal symptoms without respiratory symptoms, a hallmark of COVID-19. The early onset of the disease showed nausea, vomiting, and heartburn nine days before admittance, causing the patient not to suspect COVID-19 and also causing a delay in the patient seeking treatment. In comparison, the patient had DM, which is linked to a higher risk of severe and most often critically fatal COVID-19.[13] The time of onset to the time of admittance was delayed significantly in COVID-19 patients with gastrointestinal symptoms (9 days vs. 7.3 days) compared to patients without gastrointestinal symptoms at the beginning of the disease.[14]

The fecal-oral route usually transmits gastrointestinal infection caused by SARS-CoV-2. SARS-CoV-2 inserts the host's cell through the

Table 2. Follow-up laboratory results in the emergency room and inpatient

Parameter	08/06/2020 Day-1	13/06/2020 Day-6	18/06/2020 Day-11	22/06/2020 Day-15	26/06/2020 Day-19	30/06/2020 Day-23	Reference Range
Complete blood count							
Hemoglobin	**17(↑)**						12 - 16 g/dL
Hematocrit	48.90						40 - 50%
Leukocyte	6600						4000 - 10000/mm^3
Thrombocyte	264000						150000 - 450000/mm^3
Erythrocyte	**6.39 (↑)**						4.5-5.5 million/µL
MCV	**76.5(↓)**						80 - 90 fL
MCH	26.60						27 - 31 pg
MCHC	34.80						32 - 37 %
Diff count							
Basophil	--						0 - 1%
Eosinophil	--						1 - 6%
Neutrophil	66.60						50 - 70%
Lymphocyte	30.30						20 - 40%
Monocyte	--						2 - 10%
Clinical chemistry							
Albumin	4.87						3.5-5.0 gr/dL
AST (SGOT)	**67(↑)**						10-40 U/L
ALT (SGPT)	**102(↑)**						10 - 55 U/L
Ureum	15						13 - 43 mg/dL
Creatinine	0.7						0.6-1.4 mg/dL
Random blood glucose	209(↑)						71 - 140 mg/dL
HbA1C	**8.6(↑)**						3 – 6.5%
Uric cid	4.6						3.6 – 8.5%
Cholesterol total	193						<200 mg/dL
Cholesterol-HDL	**27(↓)**						40 - 60 mg/dL
LDL	**142(↑)**						<130 mg/dL
Triglyceride	**228(↑)**						<150 mg/dL
Rapid SARS-CoV-2							
IgM SARS CoV-2	Non-reactive						Non-reactive
IgG SARS CoV-2	**Reactive**						Non-reactive
TCM/PCR SARS CoV-2	**Positive**	**Positive**	**Positive**	**Positive**	Negative	Negative	Negative

Angiotensin-Converting Enzyme II (ACE2) membrane receptor that binds to protein S (spike) of SARS-CoV-2, which is expressed in the epithelial cells of the gastric glands, duodenum, pancreas, erythrocytes in the ileum and colon till the rectum. ACE2 staining is rarely found in the esophagus mucosa; this is probably due to the esophagus having more squamous epithelial cells, while the cells that express more ACE1 are gland cells. Various studies have identified SARS-CoV-2 RNA in the feces of the infected patient.[15,16] After the enterocytes are infected, the permeability of the cell walls towards pathogens will increase, and virus replication will take place in the epithelial cells of the GI tract. Further invasion of the enterocytes will cause malabsorption, causing enteric symptoms in the early stages of COVID-19.[17] membrane cell ACE2 receptor and nucleocapsid protein staining of the SARS-CoV-2 virus will show that even though the RNA virus is also detected in the esophageal mucosal tissue, no staining of the virus nucleocapsid protein in the esophageal mucosal tissue shows that virus infection is low in this area. The RNA and specific protein of the virus are synthesized in the cytoplasm, forming a new virion post-entry of the virus. Positive detection of the RNA of the virus in feces shows that infectious virions are secreted from gastrointestinal symptoms cells infected by the virus. Isolation of SARS-CoV-2 from feces (data unpublished, 2020) confirms the release of infectious virions to gastrointestinal symptoms. Fecal oral transmission can be an additional route for the spread of the virus and prevention of fecal-oral transmission should be considered to control the virus's spread. [17]

Clinical manifestations that occur in various organs are estimated to be in line with research results that show ACE2 expression in different tissue and organs of the body other than the respiratory

system, causing clinical symptoms that are not specific to COVID-19, according to the place of infection, so that there is an interaction between SARS-CoV-2 and ACE2 receptors of specific tissue and organs, clinical manifestations will be following the affected tissues/organs.[17]

This patient can be classified in COVID-19 with clinical symptoms but without respiratory symptoms and has a good prognosis. Comorbidities in this patient were random blood glucose of 209 mg/dL and HbA1c of 8.6%, so the patient was diagnosed with uncontrolled DM, with an increase of transaminase enzymes (SGOT 67 IU/L and SGPT 102 IU/L) and hypertriglyceridemic 228 mg/dL. HbA1c describes a person's blood sugar control in the previous two or three months. A patient with DM will be more at risk of infection if HbA1c levels are not controlled. HbA1c less than 95% is still not deemed as immunocompromised. An increase in transaminase enzymes is caused by a hepatobiliary injury that involves the cytopathic effect of SARS-CoV-2, where the S1 protein links to the ACE2 receptor in cholangiocytes and hepatocytes.[18] High glucose levels for more than two weeks can disrupt the body's immune system. In all COVID-19 patients treated in the hospital, patients with diabetes or uncontrolled hyperglycemia have four times increased mortality rate compared to patients without DM (28% vs 6.2%, $p < 0.001$).[19]

The patient came to the hospital after experiencing symptoms for nine days with the onset of infection 14 days before, causing the IgM SARS-CoV-2 antibody to be replaced with the IgG SARS-COV-2 Ab that lasts longer in the blood compared to IgM, approximately 34–41 days post-symptoms onset.[20] IgG SARS-CoV-2 IgG antibody rapid test was reactive in this patient, in line with a positive TCM SARS-CoV-2 with a Ct of 18 for gen N and 20.3 for gen E, showing a medium viral load. The viral load is in reverse with Ct-values of RT-PCR SARS-CoV-2. This patient was confirmed with RT-PCR during the 2nd week of symptoms. SARS-CoV-2 viral load increases and progresses in the early stages of the disease and decreases in recovery.[21] The severity of COVID-19 symptoms is associated with a low Ct-value and increases as the condition improves. One of the independent factors of the elongation of viral shedding causes the virus to stay longer in the host body.[22,23]

The duration the virus stays in the host body variates, and the variation of viral shedding duration can be seen as the duration from the first day of symptoms till the RNA SARS-CoV-2 becomes negative on RT-PCR examination (negative conversion). Qi *et al.* reported that the length of negative conversion in 61 patients confirmed with COVID-19 is six days minimal after the onset of symptoms, while the longest was 47 days.[24] Twenty percent of patients from the viral shedding > 17 days group experienced negative conversion after 22 days of symptoms onset. Hu *et al.* showed a faster conversion at four days and the longest at 25 days, with a median conversion of 14 days (10–18).[25] Negative conversion was usually seven days after onset 10.2%, 14 days 62.7%, and 21 days 91.2%. Not one person of all the patients with severe symptoms had a conversion in the first seven days.[25] Virus duration was also longer in elderly patients> 60 years old and in a male patient.[26]

The clinical course of this patient was relatively stable. The patient was dismissed after getting better and two negative consecutive PCR results on day 19 after being confirmed with COVID-19 or 28 days (4 weeks) after gastrointestinal symptoms. The prolonged duration of negative conversion is thought to be due to a high viral load of SARS-COV-2 in the early stages of the disease, DM comorbidity with uncontrolled chronic hyperglycemia, being a male, and late treatment after nine days following the first onset of symptoms.

CONCLUSION

Based on this case's analysis and laboratory results, it could be concluded that the final diagnosis for this patient was confirmed COVID-19 (non-respiratory symptomatic) with type 2 DM.

REFERENCES

1. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2020; 14(4): 513-517.
2. Chellapandi P, Saranya S. Genomics insights of SARS-CoV-2 (COVID-19) into target-based drug discovery. Medicinal Chemistry Research, 2020; 29: 1777-1791.
3. Corbet S, Larkin C, Lucey B. The contagion effects of the COVID-19 pandemic: Evidence from gold and cryptocurrencies. Finance Research Letters, 2020; 101554.
4. WHO. Naming the Coronavirus Disease (COVID-19) and the virus that causes it. WHO, 2020; 1-2.
5. WHO. Coronavirus Disease 2019 (COVID-19) situation report–42 data as reported by 10 AM CET 02 March 2020. H. A & A Practice, 2020; 14(6): e01218.
6. Liu Y, Yan L-M, Wan L, Xiang T-X, Le A, *et al.* Viral dynamics in mild and severe cases of COVID-19. The Lancet Infectious Diseases, 2020; 20(6): 656-657.

7. Fadini G, Morieri M, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. Journal of Endocrinological Investigation, 2020; 1.
8. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr, 2020; 14(4): 303-310.
9. Qi L, Yang Y, Jiang D, Tu C, Wan L *et al*. Factors associated with the duration of viral shedding in adults with COVID-19 outside of Wuhan, China: A retrospective cohort study. Int J Infect Dis, 2020; 96: 531-537.
10. Hu X, Xing Y, Jia J, Ni W, Liang J, *et al*. Factors associated with negative conversion of viral RNA in patients hospitalized with COVID-19. Science of the Total Environment, 2020; 138812.
11. Zheng S, Fan J, Yu F, Feng B, Lou B, *et al*. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang Province, China, January-March 2020: Retrospective cohort study. BMJ, 2020; 369.
12. Susilo A, Rumende C, Pitoyo C, Santoso WD, Yulianti M, *et al*. Coronavirus disease 2019: Review of current literatures. Jurnal Penyakit Dalam Indonesia, 2020; 7(1): 45-67.
13. Chen Y, Chen L, Deng Q, Zhang G, Wu K, *et al*. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol, 2020; 92(7): 833-840.
14. Ollarves-Carrero MF, Rodriguez-Morales AG, Bonilla-Aldana DK, Rodriguez- Morales AJ. Anosmia in a healthcare worker with COVID-19 in Madrid, Spain. Travel Med Infect Dis, 2020; 35: 101666.
15. WHO. Clinical management of COVID-19: Interim guidance, May 27th 2020. World Health Organization, 2020; 16-17.
16. Orioli L, Hermans MP, Thissen J-P, Maiter D, Vandeleene B, Yombi J-C. COVID-19 in diabetic patients: Related risks and specifics of management. Annales d'Endocrinologie, 2020; 81(2): 101-109.
17. Pan L, Mu M, Yang P, Sun Y, Wang R *et al*. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. Am J Gastroenterol, 2020; 115(5): 766-773.
18. McGrowder DA, Miller F, Cross MA, Jackson LA, Bryan S *et al*. Abnormal liver biochemistry tests and acute liver injury in COVID-19 patients: Current evidence and potential pathogenesis. Disease, 2021; 9(50): 1-24.
19. Wang W, Xu Y, Gao R, Lu R, Han K, *et al*. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA, 2020; 323(18): 1843-1844.
20. Ma H, Zeng W, He H, Zhao D, Jiang D *et al*. Serum IgA, IgM, and IgG responses in COVID-19. Cellular & Moleculer Immunology, 2020; 17: 773-775.
21. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, *et al*. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. Gastroenterology, 2020; 159(1): 81-95.
22. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology, 2020; 158(6):1831-e1833.
23. Sacks LJ, Pham CT, Fleming N, Neoh SL, Ekinci EI. Considerations for people with diabetes during the Coronavirus Disease (COVID-19) pandemic. Diabetes Research and Clinical Practice, 2020; 166: 108296.
24. Yu F, Yan L, Wang N, Yang S, Wang L, *et al*. Quantitative detection and viral load analysis of SARS-CoV-2 in infected patients. Clin Infect Dis, 2020; 10.
25. Zou L, Ruan F, Huang M, Liang L, Huang H, *et al*. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med, 2020; 382(12): 1177-1179.
26. Tepasse PR, Hafezi W, Lutz M, Kühn J, Wilms C, *et al*. Persisting SARS-CoV-2 viraemia after rituximab therapy: Two cases with fatal outcome and a review of the literature. British Journal of Haematology, 2020; 190(2):185-188.