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WORD COUNT	2023	TIME SUBMITTED	13-MAY-2022 02:06PM
		PAPER ID	85887595

Name of Journal: *World Journal of Virology*
Manuscript NO: 74421
Manuscript Type: CASE REPORT

COVID-19 presenting with persistent hiccup and myocardial infarction in a peritoneal dialysis patient: A case report

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Abstract

BACKGROUND

Persistent hiccups, lasting more than 48 h, have been described as an atypical presentation of coronavirus disease 19 (COVID-19) in the general population. To the best of our knowledge this is the first report of persistent hiccups and non-ST elevation myocardial injury (NSTEMI) as an atypical presentation of COVID-19 in a peritoneal dialysis (PD) patient.

CASE SUMMARY

A 70-year old male, who had been on PD for three years with a history of ischemic heart failure and reduced ejection fraction, presented for a scheduled radionuclide myocardial scan. Upon arrival he complained of anorexia, nausea for five days and unremitting hiccups for the previous 48 h. Clinical and laboratory examination revealed a NSTEMI plus a positive nasopharyngeal reverse transcriptase polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2. COVID-19 Lung involvement was mild and was resolved without specific treatment. Myocardial injury was managed with coronary catheterization and stenting, while hiccups responded only to baclofen *per os*.

CONCLUSION

Persistent hiccups and NSTEMI can be an atypical presentation of COVID-19 in peritoneal dialysis patients, may be due to involvement of central nervous system and myocardial injuries.

Key Words: COVID-19; Peritoneal dialysis; Atypical presentation; Hiccup; Myocardial infarction; Baclofen; Case report

Bacharaki D, Giannakopoulos P, Markakis K, Papas C, Theodorou A, Zoi V, Tsivgoulis G, Lionaki S. COVID-19 presenting with persistent hiccup and myocardial infarction in a peritoneal dialysis patient: A case report. *World J Virol* 2022; In press

Core Tip: A 70-year old male with end-stage kidney disease on peritoneal dialysis, presented for a scheduled myocardial scan due to ischemic heart failure. Upon arrival he complained for persistent hiccups during the last two days along with anorexia and vomiting for the last five days. He was diagnosed with coronavirus disease 19 (COVID-19) and non-ST elevation myocardial infarction (NSTEMI). Hiccups and NSTEMI are postulated to represent atypical COVID-19 manifestations involving the nervous system and the heart.

INTRODUCTION

The usual presentation of coronavirus disease 19 (COVID-19) includes fever and cough in the general population and in dialysis patients[1]. Gastrointestinal symptoms including anorexia, nausea and vomit have also been described, although more rarely than in chronic renal patients[2]. Persistent hiccups, *i.e.*, lasting more than 48 h, have been infrequently described in the general population with COVID-19[3,4]. To the best of our knowledge, this is the first case of COVID-19 presentation with persistent hiccups and non-ST elevation myocardial injury (NSTEMI) in a peritoneal dialysis (PD) patient.

CASE PRESENTATION

Chief complaints

A 70-year-old male with end-stage kidney disease (ESKD) maintained on PD, presented in April 2021 for a scheduled myocardial scan, having ischemic heart failure with reduced ejection fraction (35%). Upon arrival he complained for anorexia, nausea and vomit tendency and unremitting hiccups.

History of present illness

Gastrointestinal (GI) symptoms started five days before and persistent hiccups two days before, preventing him from eating and considerable sleeping. He denied any abdominal pain, stool change, cloudy PD fluids, fever, chest discomfort, symptoms suggestive of gastroesophageal reflux, or change of his custom PD regimen. His outward medication included metoprolol, monosorbide, ramipril, simvastatin/ezetimibe, furosemide, acetylsalicylic acid, pantoprazole, folic acid and darbepoetin injections. He denied any new drug initiation or new dietary habits.

History of past illness

His past medical history was significant for cardiorenal syndrome following myocardial infarction on 2000, with coronary angioplasty and stent insertion, arterial hypertension, dyslipidemia and a recent diagnosis (one month) of seronegative rheumatoid arthritis. Notably, fifteen days prior to presentation he had been admitted due to anemia (hemoglobin fall to 7.7 g/dL), nausea and appetite loss, all attributed to recent initiation of leflunomide 10 mg daily for rheumatoid arthritis. At that time C reactive protein was 141 mg/L (reference < 6 mg/L), white blood cell count 6280/µL, serum urea 89 mg/dL, creatinine 6.5 mg/dL, ferritin 642 ng/mL.

He was managed with red blood cells infusions and discontinuation of leflunomide. He was discharged in two days with Hb 9.4 g/dL, stable troponin high sensitive 209 pg/mL (reference < 14 pg/mL, while the patient's troponin high sensitive routine assessment values were between 255-430 pg/mL), free of gastrointestinal symptoms, with good appetite and negative nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Personal and family history

ESKD due to cardiorenal syndrome. PD initiated 3 years ago. Carpal tunnel syndrome diagnosed 1 year ago. Former truck driver. No special family history.

Physical examination

Physical examination revealed weight loss of nearly 2 kg (74 kg), temperature of 36.5 °C oxygen saturation 98% on room air and low blood pressure (117/73 mmHg, heart rate 90 beats per minute in sitting position). No signs of peripheral edema nor pulmonary congestion were noted. Abdominal examination was negative, as was heart and lung auscultation. The patient appeared ill with persistent hiccups, weakness, anorexia and vomit tendency, in contrast with his relatively good clinical condition on discharge 13 d before.

Laboratory examinations

Peritoneal dialysis fluids analysis revealed normal cytology and biochemistry and negative gram stain. Serum laboratory examination revealed C reactive protein of 36.8 mg/L, hemoglobulin of 9.8 g/dL, white blood count 4530/μL (neutrophils 58%, lymphocytes 28%), stable serum urea and creatinine, ferritin 855 ng/L, but troponin elevation to 1650 pg/mL.

Electrocardiography showed sinus rhythm with left bundle branch block, not different compared to previous tracings while echocardiography revealed worsening of ejection fraction to 25%. Routine nasopharyngeal RT-PCR was arranged upon admission revealed positive result he was transferred to the COVID clinic.

Imaging examinations

Due to severe co- morbidities and a positive RT-PCR for SARS-CoV-2, a chest computed tomography was performed showing signs of mild COVID-19 pneumonia, *i.e.*, less than 10% degree of lung infiltration in the right upper lobe, as small areas of ground glass opacities and small areas of atelectasis (Figure 1).

FINAL DIAGNOSIS

Mild COVID-19 pneumonia. NSTEMI. Persistent hiccups due to SARS-CoV-2 nervous system involvement.

TREATMENT

Due to mild pneumonia he did not receive any specific treatment for COVID-19. Regarding NSTEMI, he received dual antiplatelet therapy and Enoxaparin subcutaneously in a daily basis. He continued his usual ambulatory peritoneal dialysis regimen of four daily glucose – based PD exchanges, 2000 mL each (glucose 1.5% and 2.25% alternating) with a daily ultrafiltration of 1000-1200 mL. Due to persistent hiccups and anorexia that prevented him from eating and drinking he received intravenously one liter of semi-isotonic glucose solution daily with potassium supplementation. Metoclopramide injections three times per day were prescribed for hiccups and then replaced by Chlorpropamide 25 mg three times per day after 2 d of intractable hiccups. On the 7th day Baclofen tab was given orally, at a dose of 10 mg *per os* daily for 5 d.

OUTCOME AND FOLLOW-UP

Upon initiation of baclofen tab, hiccups improved significantly and they ceased completely within 48 h. As a result, the patient was able to eat and sleep, claiming to be in good condition despite NSTEMI and COVID-19. He remained euvolemic with stable arterial pressure records around 110/70 mmHg, 70 pulses/min. He did not experience any chest discomfort and his troponin values gradually fell to previous baseline levels. Maximum temperature was 37.3 °C but oxygen saturation remained stable at 98% on room air.

A coronary angiogram was performed on the 12th day of hospitalization (on negative COVID-19 PCR), which revealed a significant stenosis at the proximal segment of the first obtuse marginal branch, while previous stent was intact. A coronary angioplasty was performed one month later with stent implantation and recovering of ejection fraction to 35%.

DISCUSSION

This patient presented for as scheduled appointment, complaining of nausea, anorexia and unremitting hiccups. He had not changed his PD regimen, nor his dietary habits, or medical prescription. Clinical assessment revealed NSTEMI and mild COVID-19 pneumonia of the upper right lobe. Unremitting hiccups remained his main problem while hospitalized.

Hiccup is caused by diaphragmatic muscle contractions with early glottis closure terminating inspiration. Its pathogenesis is still obscure but lately is considered a deranged neural loop connecting brain stem and diaphragms[5]. Persistent hiccups, lasting more than 48 h, have been associated with central nervous system, cardiovascular, thoracic, metabolic and gastrointestinal disorders[5].

Uremia as a potential cause of gastrointestinal symptoms and/or hiccups was excluded, due to stable biochemical parameters and unchanged urinary output or PD regimen. Electrolyte and acid base disturbances were absent. Other potential cause of persistent hiccups could be gastro-esophageal reflux[6], which is a common complication of PD[7], but the symptoms were missing. Pneumonia by common pathogens[8] as well as by SARS-CoV-2[3,4] has been reported as a cause of persistent hiccups. Interestingly, apart from cases of lower lobe pneumonia, which would suggest direct irritation of the diaphragm as a potential mechanism resulting in hiccups[8], the association of persistent hiccups with COVID-19 has increasing publications with other sites of lung involvement[9]. Noteworthy our patient had only minor infiltration in the upper lobe in chest computed tomography (Figure 1). Persistent hiccups have also been reported as an associated symptom in cases of myocardial infarction, primarily in the inferior myocardial wall, thus in proximity with the diaphragm, speculating that hiccups could be triggered by irrigation of the phrenic nerves or alternatively by the vagus nerve supplying the pericardium, but rarely as the only presenting symptom[10]. There is a case report of persistent hiccups as atypical presentation of non-ST elevation myocardial injury[11]. In our case there was a gradual fall of cardiac troponin levels while the hiccup was still persisting, responding eventually only to baclofen. The

stenosed vessel, as revealed by angiography, (the proximal segment of the first obtuse marginal branch) perfuses the infero-lateral myocardial wall.

Furthermore, nausea and vomiting can be associated symptoms of myocardial infarction[12] and more rarely the presenting symptom in atypical cases[13].

On the other hand, there are numerous reports associating myocardial injuries and infarctions with COVID-19, potential causes being direct myocyte injury and prothrombotic effect of SARS-CoV-2 infection[12]. Nevertheless, it is still difficult to differentiate between non-COVID acute coronary syndrome and COVID-19 induced acute myocardial injury[14]. Noteworthy, gastrointestinal symptoms, as diarrhea (more often) nausea and vomiting often accompany COVID-19, either by direct infection of GI cells or indirectly[15], although diarrhea was absent in our patient. Since the underlying mechanisms of persistent hiccups are various disorders (structural, infectious, and inflammatory) that impact either the central nervous system or the phrenic nerves or their branches[16], one could speculate that COVID-19 could be linked causally with hiccups by nervous system involvement[17].

Baclofen is a gamma-aminobutyric acid B receptor agonist approved as a medication to control spasticity[18]. It has been used successfully for persistent hiccups of different etiologies with an action attributed to either reduction of dopamine release in the central nervous system, which could interrupt hiccup's reflex arc or induction of transient lower esophageal sphincter relaxations, by stimulating gamma-aminobutyric acid B receptors of the motor nucleus of the vagal nerve and nucleus tract solitarious[18]. Hiccups attributed to COVID-19 have been managed with hydroxychloroquine, metoclopramide, chlorpropamide as well as a combination scheme with baclofen included[3,4,9]. In this case hiccups did not respond to metoclopropamide nor chlorpropamide, but on the contrary had an immediate and complete response to baclofen.

Based on the above COVID-19 maybe the unifying cause of all. Anorexia, vomit tendency and hiccup could be manifestations of SARS-CoV-2 gastrointestinal[15] and/or nervous system involvement[16,17]. non-ST myocardial infraction could also be a

manifestation of COVID-19[11]. Nervous system and heart involvement could have as common pathway the COVID-19-induced endotheliitis[18].

CONCLUSION

A case of atypical presentation of COVID-19 in a PD patient with persistent hiccups and NSTEMI is described in here. We may speculate that they could be the result of SARS-CoV-2 involvement of nervous system and heart respectively. Baclofen seems to be the drug of choice for persistent hiccups even in patients with ESKD.

ACKNOWLEDGEMENTS

We acknowledge the support and contribution in the management of the COVID-19 infected patient of the nurses of Hemodialysis and Peritoneal Dialysis Unit: Irene Zorba, Dimitra Siopi, Athina Maniati, Zoi Polymerou and Lambrini Xoxakou.

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