Case Report

Remedesivir-induced newly onset type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by an elevation in blood glucose levels. During the COVID-19 pandemic, Remdesivir, an antiviral drug originally used to treat Hepatitis B, was later approved for use in COVID-19 treatment. It is important to be aware of rare but serious adverse events associated with Remdesivir therapy, particularly in patients without known comorbidities. In this report, we elaborate on a case of drug-induced Type-2 diabetes mellitus in a man who was healthy with no other comorbidities but was diagnosed with COVID-19. The patient's blood glucose levels were significantly increased with Remdesivir therapy. On withholding the drug, the patient's blood glucose levels dropped, and they elevated again once it was re-administered and continued. Therefore, it is crucial to routinely monitor the blood glucose levels in patients receiving Remdesivir therapy to avoid such adverse effects.

Key words: COVID-19, Diabetes mellitus, Remdesivir

A broad-spectrum antiviral agent, Remdesivir, was first designed in 2009 to treat Hepatitis C. Still, later in October 2020, it was licensed by the Food and Drug Administration to treat severe acute respiratory syndrome coronavirus 2 [1-3]. Existing clinical trial literature showed organ-specific adverse events such as increased liver enzyme levels, indicating liver damage, and allergic reactions that cause fever, low oxygen, and other symptoms. Other potential side effects include shortness of breath, wheezing, swelling, rash, sweating, shivering, and hyperglycemia [4].

Type 2 diabetes mellitus (T2DM) is a chronic disease that is insulin independent and characterized by high blood sugar levels. It is a metabolic disease that leads to significant damage to the kidneys and other organs [5,6]. Diabetes affects 422 million people globally, with 1.5 million deaths annually. Drug-induced diabetes mellitus is a form of secondary diabetes. The drugs that have an increased risk of developing diabetes mellitus are corticosteroids, thiazide diuretics, beta-blockers, antipsychotics, and statins [7]. According to previous studies, during COVID-19, the course of therapy, including Remdesivir, has shown a surge in sugar levels, and also, when given along with corticosteroids and other antivirals, has shown serious side effects, one of them being diabetes mellitus [8,9].

This case report examines the onset of T2DM in a previously healthy patient after treatment with Remdesivir. The observed temporal relationship, along with the patient's responses to both the de-challenge and re-challenge of the medication, suggests a potential causal connection. This case underscores the necessity for routine blood glucose monitoring during Remdesivir therapy, even in individuals without a prior history of diabetes.

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CASE PRESENTATION

A man in his late 60s was admitted to the hospital with fever, chills, and breathlessness for 6 days. The patient had no known comorbidities and had no significant social and family history.

On day 1 of hospitalization, the patient arrived with a reverse transcription-polymerase chain reaction positive report from an outside laboratory, and on general examination, the patient was conscious and coherent. On physical examination, the findings were: blood pressure: 130/80 mmHg; pulse rate: 116 bpm; and oxygen saturation: 90% without oxygen support. The patient's peripheries were warm, and the cardiovascular and respiratory examinations were normal.

Day 1 investigations were normal, and the patient's glucose level was 119 mg/dL, and the HbA1c was 5% when checked with a capillary blood glucose (CBG) meter. On further examination, the patient had undergone a Chest X-ray, where the report was presented with Pneumonitis. Based on the objective and subjective evidence provided, the patient was diagnosed with COVID-19-positive with Pneumonitis.

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To treat COVID-19 with Pneumonitis, on day 1, the patient was given the following medications: Cefoperazone + Sulbactam, Vecuronium Bromide, Doxycycline + *Lactobacillus*, Ivermectin, Pantoprazole, and Paracetamol. The patient was initiated on 4 L of oxygen support through a simple face mask to maintain the oxygen saturation level. Taking consent from the patient, he was administered intravenous Remdesivir 200 mg in 250 mL of normal saline STAT over 2 h as a loading dose on day 1, followed by 100 mg in 100 mL of normal saline over 1 h as a maintenance dose from day 2, along with the other medications. On day 2, the patient developed hyperglycemia with CBG: 413 mg/dL. The patient's CBG levels were being monitored daily every 8 h, and the glucose levels were constantly fluctuating in the high range (Fig. 1), considering the patient does not have a known case of T2DM. With this evidence, including an HbA1c level of 8.1%, the patient was diagnosed with newly onset T2DM on day 4. On day 6, Remdesivir was de-challenged, followed by a reduction in CBG level: 180 mg/dL the next day. The drug was re-challenged on day 8, after observing a reduction in CBG level. Later, the patient was given an Injection of human insulin 20-20-20 U subcutaneously to treat newly onset T2DM. To treat newly onset T2DM, the patient was given an injection of human insulin 20-20-20 U subcutaneously until the blood glucose level was normalized. This reaction was attributed to the suspected drug, Remdesivir.

The patient received a 7-day course of Remdesivir to treat COVID-19. Injection Human Actrapid was given to the patient to treat T2DM which may be attributed to Remdesivir, on hospitalization. After 9 days of hospitalization, the patient's health status improved, his CBG level was found to be 252 mg/dL on discharge, and he was prescribed an oral antihyperglycemic agent, discontinuing the injection of Human Actrapid since the patient was newly diagnosed with T2DM. On regular telephonic follow-ups, it was found that the patient is still on oral antihyperglycemic agents.

DISCUSSION

A range of pharmacological substances impact the maintenance of glucose levels in the body, leading to either low blood sugar levels (hypoglycemia) or high blood sugar levels (hyperglycemia). The modifications in the serum glucose levels caused by medication can have long-lasting consequences on the functioning of the human body [10]. Several coexisting medical conditions that elevate the susceptibility to severe illness for COVID-19 have been documented, encompassing hypertension, cardiovascular disorders, diabetes mellitus, and obesity [11].

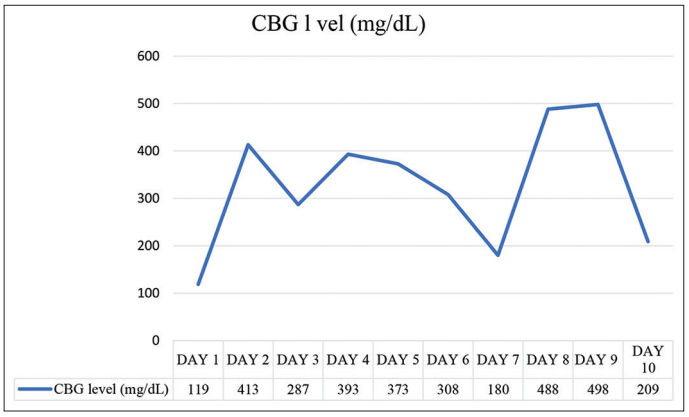

Figure 1: Capillary blood glucose levels

Multiple mechanisms exist through which common therapeutic agents influence glucose metabolism, including pancreatic, hepatic, and peripheral effects [12-14]. New-onset diabetes has been strongly linked to combined antiretroviral therapy. In particular, it has been associated with short-term exposure to stavudine, indinavir, and didanosine [15].

During the peak of the COVID-19 pandemic, there were no officially approved targeted treatments available. Remdesivir, as a nucleotide prodrug, provided a potential solution for urgent emergency therapies, and, in the context of treating COVID-19, its anticipated benefits were deemed to outweigh the associated risks, positioning it as a potential treatment. In the initial phase of the pandemic, the medication underwent clinical trials to evaluate its safety and effectiveness. Subsequently, the FDA granted an emergency use authorization, permitting its utilization in COVID-19 patients as needed [16,17]. According to the COVID-19 treatment guidelines, when a patient is hospitalized requiring conventional oxygen, Remdesivir is administered to the patient with the steroid, dexamethasone [18]. Steroids function similarly to cortisol, the stress hormone produced by the adrenal glands. They impact insulin sensitivity and the body's insulin response. When cells do not respond appropriately to insulin, it leads to consistently elevated blood sugar levels, and if left unaddressed, may result in diabetes [19].

In a trial performed in mice fed a high-fat diet, Remdesivir reduced hyperglycemia, insulin resistance, and fatty liver [20]. Clinical trials assessed blood glucose levels in Remdesivir-treated groups compared to placebo groups and Chinese patients. However, more evidence is needed to fully understand its effect on glucose metabolism. Notably, adverse events were similar between the Remdesivir and placebo groups, except for slightly higher rates of pyrexia and hyperglycemia in the Remdesivir group [21].

Our patient's clinical and laboratory presentations met the criteria for newly onset T2DM, which occurred after the course of Remdesivir for the treatment of COVID-19 pneumonia. While the patient received conventional oxygen, Remdesivir was administered as stated by the COVID-19 treatment guidelines. However, due to increased glucose levels, Remdesivir was discontinued. After a temporary reduction in glucose levels, Remdesivir was resumed. However, subsequent elevated glucose levels suggest that this reaction could be linked to the drug Remdesivir.

CONCLUSION

This case highlights a rare but important side effect of Remdesivir therapy, which is newly onset T2DM in a previously healthy individual. It emphasizes the need for careful monitoring of

blood glucose levels in patients receiving Remdesivir, even in the absence of known risk factors for diabetes. Early detection and prompt management of hyperglycemia can help prevent complications and ensure better patient outcomes.

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