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Coxsackie's Deadly Surprise: When a Common Virus Leads to a Life-Threatening Coma

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Introduction

Hand-foot-and-mouth Disease (HFMD) is caused by the Coxsackie virus. The infection is most commonly seen in children under the age of 10 years. Known long-term complications associated with the Coxsackie virus are chronic fatigue and myocarditis. Hyperglycemic hyperosmolar state (HHS), characterized by severe hyperglycemia, hyperosmolarity, and altered mental status, is a life-threatening complication of diabetes mellitus. Commonly precipitated by factors such as infection, non-adherence to medications, or comorbidities. Here, we present an exceptional case of HHS in a 44-year-old male with prediabetes associated with Coxsackie virus infection, highlighting the diagnostic and management challenges posed by this uncommon presentation.

Case Presentation

A 44-year-old male patient was admitted to the hospital for progressively worsening abdominal pain, nausea, vomiting, and poor oral intake for 2 weeks associated with 40 pounds of weight loss, lethargy, and confusion since one day before admission. His medical history is significant only for controlled hypertension on amlodipine 5 mg daily, pre-diabetes not on any medications (HgbA1C 6.3% in early 2023), and sick contacts with upper respiratory tract infection (URTI) in the family. A recent test-proven Coxsackie virus B (CVB) URTI by a throat swab when he had lesions in palms, buccal mucosa along with fever, and URTI symptoms 4 weeks prior. He has recovered well from those symptoms within 2-3 days however, 2 weeks later he began feeling ill again with the complaints mentioned above. Upon admission, he was found to have new-onset profound hyperglycemia with sugars of the 1600s (figure 1) with no anion gap or acidosis (figure 2) and mildly elevated ketones. Workup initiated for gastrointestinal (GI) pathology was negative including a computerized tomography (CT) abdomen which revealed no significant intra-abdominal pathology. Endocrinology was consulted for the management of new-onset HHS and the patient was started on intravenous fluids and insulin. He was subsequently intubated for continued worsening alteration in mental status. He remained on a mechanical ventilator for 4 days and underwent extensive workup including a magnetic resonance imaging (MRI) brain which was negative for acute intracranial pathology including lack of cerebral edema. A spinal tap was performed for cerebrospinal fluid (CSF) studies which were negative for the infectious etiology of altered mental status. CSF cytology was negative for malignant cells. The CSF analysis (figure 3) and studies included an unremarkable Meningitis Encephalitis panel by PCR methodology, and negative routine bacterial cultures, negative mycobacteria, and fungal stains with pending final cultures. His transthoracic echocardiogram (TTE) revealed reduced left ventricular ejection fraction (LVEF) to 45-50% with mild global wall hypokinesis. Hemoglobin A1c was found to be >15.5% (<5.7%), low C peptide of 0.4 (1.1-4.4), and Insulin antibodies were negative at <5. Coxsackie virus A and B IgG antibodies elevated at 1:800 and 1:1000 respectively (figure 4). Given the negative work-up for other etiologies and positive Coxsackie serology on the background of recent URTI, he was ultimately diagnosed with viral myocarditis, cardiomyopathy, and possible autoimmune pancreatitis resulting in type I diabetes mellitus. He responded well to the medical treatment, was extubated, and returned to his baseline mental and physical status after 5 days of controlled sugars with insulin and was eventually discharged home with no additional needs except follow-up with endocrinology for management of new-onset diabetes.

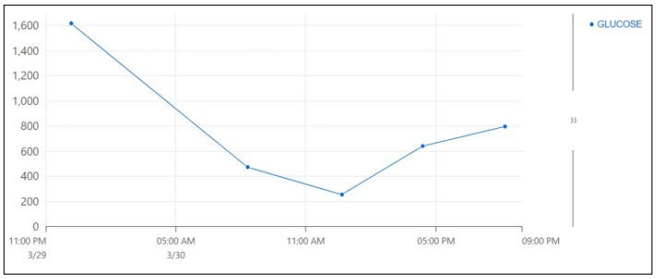

Figure 1: Graph Demonstrating the Trend of Patient's Sugar Levels

	Levels upon admission	Levels upon Discharge	Reference Range
Serum Glucose	1617 mg/dL	227 mg/dL	70-99 mg/dL
Serum Biarbonate	24 mmol/L	22 mmol/L	21-31 mmol/L

Figure 2: Table Comparing Serum Glucose and Bicarbonate Levels Upon Admission and Discharge

	CSF Analysis	Reference Range
Color	colorless	colorless
Appearance	clear	clear
WBC	4	0-6/mm3
RBC	6	0/mm3
Protein	54	15-60 mg/dL
Glucose	224	50-80 mg/dL

Figure 3: Cytology

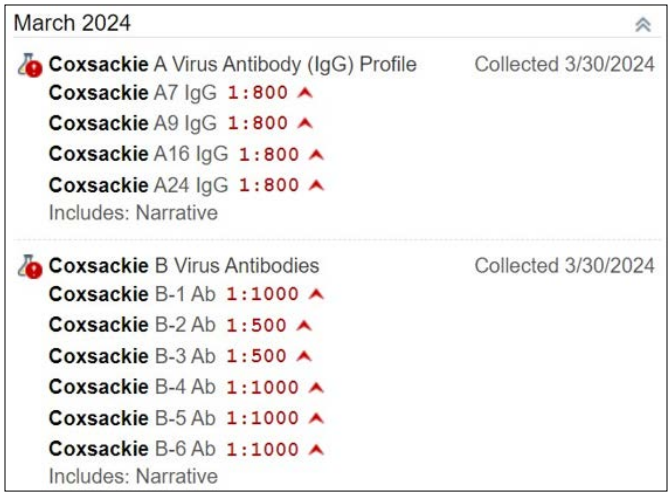

Figure 4: Coxsackie Antibody Levels After 4 Weeks of URTI Symptoms

Discussion

While HHS is frequently associated with factors such as infection, stress, or medication non-compliance, the role of viral infections, particularly the CVB, in its pathogenesis, is less commonly recognized. CVB belongs to the Enterovirus genus and is known to cause a spectrum of clinical manifestations, ranging from mild febrile illness to severe systemic complications. It has been reported that CVB persists in the gut, blood cells, and thymus. These locations may act as reservoirs for pancreatic infection or reinfection, and the persistence of CVB may contribute to the disruption of β-cell tolerance [1].

The Coxsackie virus may induce insulin resistance and pancreatic beta-cell dysfunction, leading to uncontrolled hyperglycemia and the development of HHS in susceptible individuals, such as those with pre-existing diabetes mellitus. The known long-term complications with the Coxsackie virus include myocarditis and chronic fatigue. One of the hypothesized mechanisms such as the virus triggering an autoimmune attack on the mitochondria in the heart, creating chronic fatigue and myocarditis. We theorize that HHS could be caused in the setting of inadequate immune protection, and beta-cell mortality may be predominantly caused by Coxsackie or secondary to T-cell responses against beta cells infected with the virus. It has also been proposed that epitope-mimicking processes may be involved in the skewing of the physiological antiviral response toward autoimmune [2].

In a recent study done in 2021 comparing vaccinated versus unvaccinated mice, these studies demonstrated that CVB vaccines did not modify islet cell inflammation in an animal model exhibiting spontaneous autoimmune type 1 diabetes. However, they exhibit efficacy in preventing CVB-induced disease progression within the same model [3]. However, an old study done in 2002 on mice showed contradictory evidence that CVB is indeed protective for type 1 diabetes and lowers the incidence when compared to the mice group that does not have CVB [4]. More research and studies in human subjects are needed to understand the pathophysiology and correlation of Coxsackie B virus and the development of Islet cell dysfunction/ development of diabetes mellitus.

In our case, the temporal association between the onset of hyperglycemic symptoms and the detection of Coxsackie virus IgG antibodies in 4 weeks, preceded by a test-proven Coxsackie URTI by throat swab polymerase chain reaction (PCR) suggests a potential causative link.

Conclusion

This case highlights the importance of considering viral etiologies in the differential diagnosis of hyperglycemic emergencies, particularly in patients with underlying diabetes mellitus or prediabetes. Clinicians should maintain a high index of suspicion and inquire about recent illnesses to account for Coxsackie virus infection in patients presenting with HHS, especially in patients with recent lesions of the buccal mucosa, and a collateral history of sick close contacts with URTI. Further research is warranted to elucidate the significant association between the Coxsackie virus and hyperglycemic complications, paving the way for targeted therapeutic interventions and improved patient outcomes.

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