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A Rare Case of Insulinoma in a Patient with Hydrocephalus and COVID-19

Un caso raro de insulinoma en un paciente con hidrocefalia y COVID-19

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SUMMARY

Insulinoma is a rare entity, in which neuroglycopenia symptoms of recurrent hypoglycemia are often confused with the neuropsychiatric disorder, especially in a patient with hydrocephalus. Hypoglycemia leads to a proinflammatory and procoagulant state, which may worsen the COVID-19 prognosis. We report a case of a 25-year-old woman with an initial presentation of seizure. No previous medical history and drugs were recorded. Intravenous dextrose is administered as low blood sugar was evident but no marked improvement in consciousness was observed. Later head CT scan revealed hydrocephalus and brain atrophy. While intracranial lesion was thought to be the reason, recurrent hypoglycemia was recorded despite meticulous partial parenteral nutrition. Plasma insulin and C-peptide test showed inappropriately high values in the hypoglycemic state (154.5 uIU/mL and 12.1 ng/mL, respectively) and lead to insulinoma, which was in accordance with the MRI result. Thorough non-operative management was commenced, and blood glucose was eventually controlled. Unfortunately, the patient developed pneumonia COVID-19 and died of respiratory failure. Diagnosis of insulinoma in hydrocephalus patients with seizures and altered levels of consciousness is challenging. Non-operative management is difficult in an unconscious patient, let alone in an isolation room. Moreover, the COVID-19 prognosis is proven to be worse in hypoglycemic patients.

Keywords: *COVID-19, hydrocephalus, hypoglycemia, insulinoma, seizures.*

RESUMEN

El insulinoma es una entidad rara, en la que los síntomas de neuroglucopenia de hipoglucemia recurrente a menudo se confunden con un trastorno neuropsiquiátrico, especialmente en un paciente con hidrocefalia. La hipoglucemia conduce a un estado proinflamatorio y procoagulante, lo que puede empeorar el pronóstico de la COVID-19. Presentamos

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el caso de una mujer de 25 años con un cuadro inicial de convulsiones. No se registraron antecedentes médicos ni fármacos. Se administró dextrosa intravenosa ya que era evidente un bajo nivel de azúcar en la sangre, pero no se observó una mejora marcada en la conciencia. Posteriormente, la tomografía computarizada de la cabeza reveló hidrocefalia y atrofia cerebral. Si bien se pensó que la causa era una lesión intracraneal, se registró hipoglucemia recurrente a pesar de una meticulosa nutrición parenteral parcial. Las pruebas de insulina plasmática y péptido C mostraron valores inapropiadamente altos en el estado de hipoglucemia (154,5 uIU/mL y 12,1 ng/mL, respectivamente) y dieron lugar a insulinoma, lo que concordaba con el resultado de la resonancia magnética. Se inició un manejo no quirúrgico minucioso y finalmente se controló la glucosa en sangre. Desafortunadamente, el paciente desarrolló neumonía por COVID-19 y murió por insuficiencia respiratoria. El diagnóstico de insulinoma en pacientes con hidrocefalia con convulsiones y niveles alterados de conciencia es un desafío. El manejo no quirúrgico es difícil en un paciente inconsciente, y mucho menos en una sala de aislamiento. Además, se ha demostrado que el pronóstico de COVID-19 es peor en pacientes con hipoglucemia.

Palabras clave: *COVID-19, hidrocefalia, hipoglucemia, insulinoma, convulsiones.*

INTRODUCTION

Insulinoma is one differential diagnosis of hypoglycemia caused by endogenous hyperinsulinism. It is a rare disease with an incidence of 1 in 250 000. Most insulinoma is benign and occurs sporadically, only less than 10 % is associated with malignancy and multiple endocrine neoplasias (MEN type-1) (1).

Glucose is the main substrate for neuron metabolism, as evident in the neuroglycopenic manifestation of hypoglycemia. Hypoglycemia must be excluded in a patient presenting with seizure and altered level of consciousness (2). However, only a few studies had reported seizures in insulinoma and only two had reported hydrocephalus in chronic hypoglycemia (3.4). According to our studies, this is the first case reporting COVID-19 in a patient with insulinoma. COVID-19 itself was detrimental to the immune system, let alone recurrent hypoglycemia that occurred in insulinoma.

CASE PRESENTATION

A 25-year-old woman was referred to the emergency room with an altered level of consciousness and focal to bilateral tonic-clonic seizure. The seizure happened about 1 minute 4-5 times a day with no recovery of consciousness in between. No previous seizures nor trauma was reported, although the family did report previous multiple syncopes one month before the seizure occurred, especially in the morning. The family denied any use of antidiabetic drugs or any other hypoglycemia-associated drug. No history of eating disorder, autoimmune disorder, diabetes, liver, cardiac, or kidney failure.

During the physical examination, a Glasgow coma scale of 8 and an increased heart rate of 110 bpm with regular rhythm were recorded, while other vital signs were unremarkable. Both pupils were isochor and showed normal light reflex. Motoric examination revealed spasticity within all extremities with no lateralization. No pathological reflex was noted.

An urgent blood glucose test indicated low blood glucose (30 mg/dL) and intravenous dextrose was given accordingly. The seizure ceased momentarily but no improvement of consciousness was observed despite the normalization of blood glucose. A Head CT scan from the previous hospital revealed brain atrophy and hydrocephalus (Figure 1), hence a ventriculoperitoneal (VP) shunt was done before referral to improve CSF flow, yet no improvement was observed. CSF analysis was unremarkable with a negative nucleic acid amplification test (NAAT) for *Mycobacterium tuberculosis*. Moreover, brain magnetic resonance angiography (MRA) showed normal results. Herpes simplex virus (HSV) antibody was negative with a normal ANA test. Electroencephalography had not been done due to the deterioration of the patient's condition. Strangely, routine blood glucose checks kept showing low blood glucose despite meticulous partial parenteral nutrition and careful drug consideration.

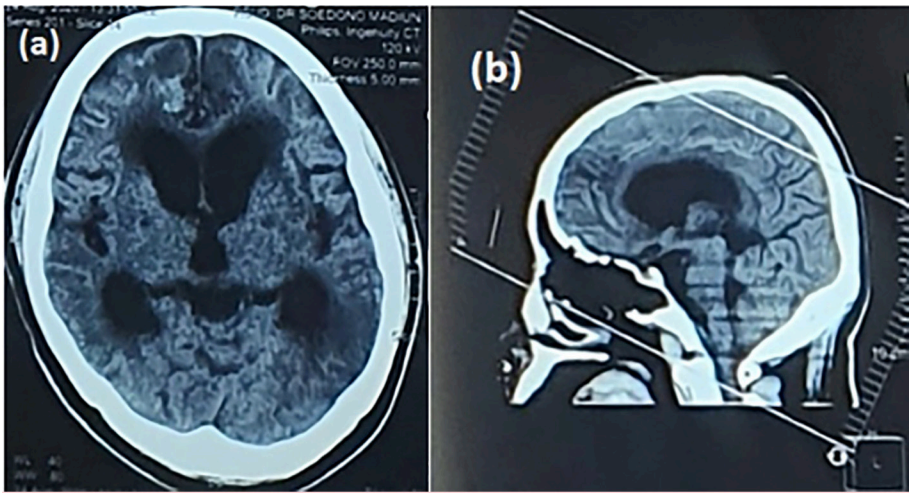

Figure 1. Head CT-scan revealed dilatation of lateral and third ventricle in axial (a) and sagittal view (b).

Insulin plasma and C-peptide levels were ordered in a hypoglycemic state (blood glucose of 45 mg/dL) and they showed inappropriately high levels (154.5 uIU/mL and 12.1 ng/mL, respectively). Later MRI abdomen resulted in a contrast-enhanced mass of 2.9 x 2 cm in the corpus of the pancreas suggestive of insulinoma (Figure 2). Metastasis was not seen in the MRI abdomen and chest CT scan. TSH and cortisol levels were also tested to rule out hormonal deficiencies, with Ca 19-9 to rule out malignancy.

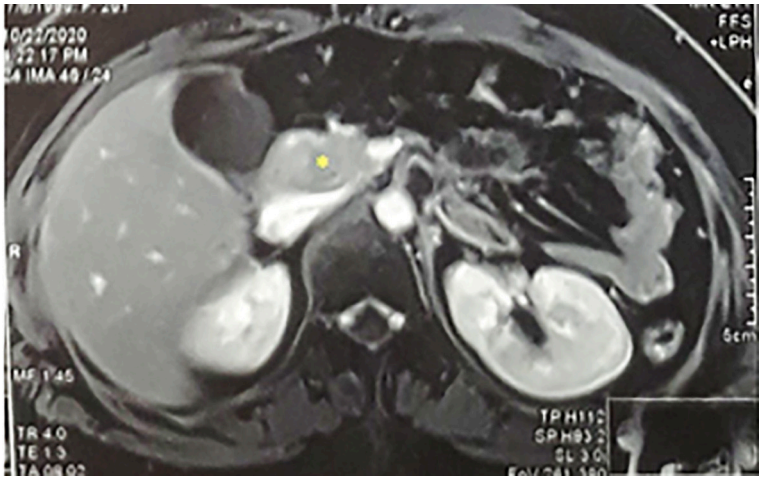

Figure 2. MRI abdomen revealed a hypointense irregular mass (yellow starred) in the pancreatic corpus 2.9x2 cm with contrast enhancement.

The complete results of the laboratory examination are shown in Table 1. An initial diagnosis of insulinoma and epileptic seizures caused by recurrent hypoglycemia was made.

Table 1. Laboratory Findings during Hospitalization

Lab Test	Result	Normal range[1]
Insulin*	154.5 uIU/mL	0.5-300 uIU/mL
C-peptide*	12.1 ng/mL	0.9-7.1 ng/mL
TSH	0.768 uIU/mL	0.55-4.78 uIU/mL
Cortisol	117.2 ng/mL	20.2-131.0 ng/mL
Ca 19-9	17.39 U/mL	<37 U/mL

*Test was done in a hypoglycemic state (BS of 45 mg/dL)
[1] Based on local laboratory references

An initial surgical plan had already been scheduled, but the patient developed respiratory distress with bilateral pulmonary infiltrates and positive PCR COVID-19 result. Therefore, surgery was canceled and the patient was transferred to the isolation room. A careful nutrition plan was arranged along with the administration of steroids, verapamil, and octreotide, in which the last failed to show any effect on the blood glucose level. The dietary plan included frequent enteral feeding of milk, fruit juices, and fructose syrup, which is quite difficult to manage in an isolation room. The parenteral fluid consisting of maltose and dextrose was also given. Three-hourly blood glucose monitoring is shown in Figure 3. Unfortunately, several days later, despite the final follow-up of PCR COVID-19 showed a negative result, and the patient died of respiratory failure.

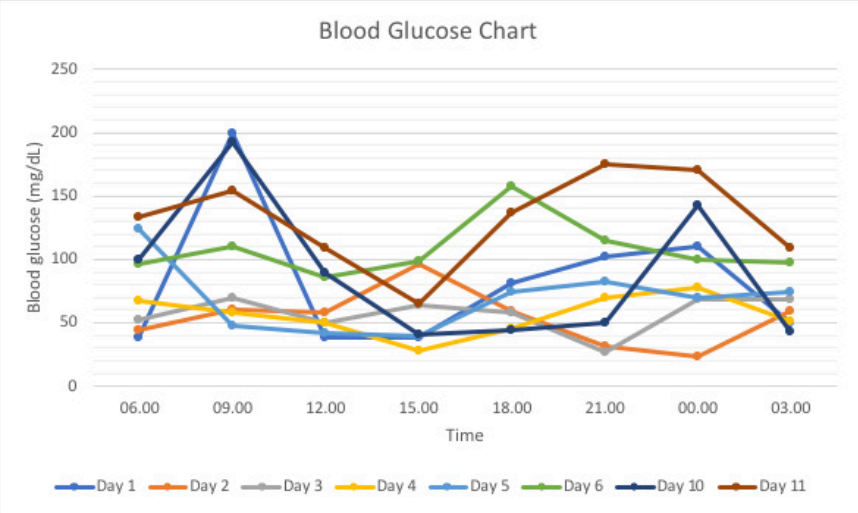

Figure 3. Blood glucose chart throughout different regimens. Day 1 consisted of diet and steroid iv. Day 2-4 subcutaneous octreotide was given in an increased dose. Day 5 octreotide was stopped, and verapamil was given enterally. Day 6 Three-hourly dextrose was administered intravenously. On day 10 patient was transferred to an isolation room. Day 10-11 no changes in glucose management therapy.

DISCUSSION

Insulinoma must be considered in a patient with recurrent hypoglycemia, as this is the prototype of endogenous hyperinsulinism. However, hypoglycemic drug usage, critical illness, and hormonal deficiency must be ruled out first. Based on its pathophysiology, diagnosis is established with failure of decreased insulin level in response to hypoglycemia. Documentation of plasma insulin concentrations of 3 uIU/

mL (18 pmol/L) or higher, plasma C-peptide concentrations of 0.6 ng/mL (0.2 nmol/L) or higher, and plasma proinsulin concentrations of 5.0 pmol/L or higher when hypoglycemic happened (blood glucose less than 55 mg/dL) is required, which was fulfilled in this case (1). CT or MRI localizes 80 % of the tumor, and MRI may be more sensitive. Endoscopic ultrasound and selective pancreatic arterial calcium injection can also be used but to a lesser extent (5).

Insulinoma is typically presented as a history of neuroglycopenia episodes, especially in a fasting state. Seizure and altered mental state are a few of the neuroglycopenic symptoms that had been reported in insulinoma, up to 17 %-23 % and 75 %-80 %, respectively (5-7). Of these reports, the initial diagnosis was neuropsychiatric disorder, which implied a challenge in diagnosing insulinoma. Moreover, Dagett (8) reported up to 7 cases of insulinoma presenting with neuroglycopenia episodes, two of those experienced altered mental consciousness and rigidity despite optimal treatment for hypoglycemia and eventually regained consciousness after the removal of insulinoma. In line with these reports, no improvement of consciousness was observed in our patient, and oddly, seizures still occurred despite blood glucose control, which lead us to false assumption of primary intracranial disorder.

No case of hydrocephalus in insulinoma had been reported, but Iino (3) and Blau (4) had reported hydrocephalus occurred in chronic hypoglycemia. Iino reported hydrocephalus developed as brain atrophy and impairment in CSF flow occurred, which was proven with ventricular reflux evident in RI cisternography. Moreover, this normal pressure hydrocephalus was only established in a repeated coma state of hypoglycemic, in which hypoglycemia brain damage developed. Endogenous neurotoxin aspartate is released and damage to white matter and periventricular reduce its elasticity properties, hence dilating the ventricle under CSF pressure (3).

Blood glucose stabilization is substantial in insulinoma. Surgery remains the first-line treatment, but for those unresectable or unable (in this case due to respiratory distress of COVID-19), diet and pharmacological including diazoxide and octreotide can be tried (1). Frequent feeding through a nasogastric tube is given to this patient, in form of milk and fruit juices. Diazoxide was not available in our hospital, so octreotide was given instead. Octreotide binds to somatostatin receptor-2, which is present in varying degrees in insulinoma (9). Hence, octreotide response is variable, as proven in our case. Glucocorticoid (9) and verapamil (10) can also be used in conjunction with other therapy in some cases. In our case, blood glucose was controlled with diet, glucose infusion, steroids, and verapamil.

Finally, hypoglycemic patients are at a 25-times risk of developing severe pneumonia COVID-19 (11). Hypoglycemia depletes the energy needed to fight acute infection. Furthermore, glucose is needed to activate immune cells and maintain the antioxidant defense system through the maintenance of glutathione (GSH). As a result, low blood sugar leads to enhanced oxidative stress and impaired immune response (11). Hyperinflammation and hypercoagulable state develop as oxidative stress is enhanced and endothelial dysfunction takes place (12), which is detrimental to COVID-19 patients. This is true as in our patient, respiratory distress occurred because of pneumonia COVID-19.

CONCLUSION

Insulinoma in a hydrocephalus patient is rare, but it must be considered in a patient with documentation of recurrent hypoglycemia. Nonoperative management is paramount in a patient unable to undergo surgery, which is challenging to manage in the isolation room. Hypoglycemia must be prevented to avoid the poor prognosis of COVID-19 in insulinoma.

Declaration of interest

The authors have declared that no competing interests exist.

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REFERENCES

1. Cryer PE, Arbalaez AM. Hypoglycemia. In: Melmed S, Auchus RJ, Goldfine AB, Koenig RJ, Rosen CJ, editors. William's Textbook of Endocrinology. 14th edition. Philadelphia: Elsevier; 2020.p.1526-1545.
2. Cryer PE, Davis SN. Hypoglycemia. In: Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's Principles Of Internal Medicine. 20th edition. Philadelphia: Elsevier; 2018.p.2883-2889.
3. Iino K, Yoshinari M, Yoshizumi H, Ichikawa K, Iwase M, Fujishima M. Normal pressure hydrocephalus in diabetic patients with recurrent episodes of hypoglycemic coma. Diabetes Res Clin Pract. 2000;47(2):105-110.
4. Blau A, Reider N, Bender MB. Extrapyramidal Syndrome and Encephalographic Picture of Progressive Internal Hydrocephalus in Chronic Hypoglycemia. Case Reports. 1936;910-920.
5. Mathur A, Gorden P, Libutti SK. Insulinoma. Surg Clin North Am. 2009;89(5):1105-1121.
6. Graves T, Gandhi S, Smith S, Sisodiya S, GS C. Misdiagnosis of seizures: Insulinoma presenting as adult-onset seizure disorder. J Neurol Neurosurg Psychiatry. 2004;75:1091-1092.
7. Bazil CW, Pack A. Insulinoma presenting as seizure disorder. Neurology. 2001;56(6):817-818.
8. Dagett P, Nabarro S. Neurological aspects of insulinomas. Postgrad Med J. 1984;60(8):577-581.
9. Lou I, Inabnet WB. Advances in the diagnosis and management of insulinoma. Adv Treat Manag Surg Endocrinol. 2019;1:199-206.
10. Khoury N, Cryer PE. Hypoglycemia. In: McGill J, Clutter W, Baranski T, editors. Endocrinology Subspecialty Consult. 3rd edition. Missouri: Wolters Kluwer Health; 2013.p.414-423.
11. Zhu B, Jin S, Wu L, Hu C, Wang Z, Bu L, et al. J-shaped association between fasting blood glucose levels and COVID-19 severity in patients without diabetes. Diabetes Research and Clinical Practice. 2020;168.
12. Kahal H, Halama A, Aburima A, Bhagwat AM, Butler AE, Grauman J, et al. Effect of induced hypoglycemia on inflammation and oxidative stress in type 2 diabetes and control subjects. Sci Rep. 2020;10(1):1-8.