AACE Clinical Case Rep. 7 (2021) 247–248

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

Insulinoma With Concomitant Insulin Antibodies

Anira Iqbal, MD [1], David T. Broome, MD [2,*], Vinni Makin, MD [2], Divya Yogi-Morren, MD [2]

[1] Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio
[2] Department of Endocrinology, Diabetes & Metabolism, Cleveland Clinic Foundation, Cleveland, Ohio

ARTICLE INFO

Article history:
Received 10 October 2020
Received in revised form
18 January 2021
Accepted 24 January 2021
Available online 3 February 2021

Key words:
insulinoma
insulin antibody
hypoglycemia
Hirata syndrome

ABSTRACT

Objective: The coexistence of insulinoma and insulin antibodies is extremely rare. The aim of this novel case report is to inform physicians of the possibility of an insulinoma with concomitant insulin antibodies.

Methods: In this report, we describe a patient with symptomatic hypoglycemia confirmed with a 72-hour fast, who was subsequently found to have an insulinoma with concomitant elevation in his immunoglobulin G insulin antibody titer.

Results: The patient presented with initial symptoms of diaphoresis, confusion, and disorientation and was found unresponsive by a bystander. He had a fingerstick blood glucose of 36 mg/dL (reference 74-99 mg/dL), without exogenous insulin or sulfonylurea use. His symptoms resolved with administration of glucose. He was subsequently admitted for a 72-hour fast in which he developed neuroglycopenic symptoms 4 hours into the fast with fingerstick glucose of 47 mg/dL and serum glucose of 44 mg/dL (reference 74-99 mg/dL), C-peptide of 10.8 ng/mL (reference 0.5-2.7 ng/mL), insulin level of 106 μIU/mL (reference <25 μIU/mL), and a proinsulin level of 675 pmol/mL (reference <22 pmol/mL). His insulin-to-C-peptide ratio was 0.20, in which a ratio <1 is indicative of an insulinoma. Endoscopic ultrasound demonstrated a 16 x 11 mm biopsy-proven neuroendocrine tumor. He was found to have a high titer insulin antibody titer at 2.4 U/mL (reference <0.4 U/mL), was started on prednisone, and underwent successful radiofrequency ablation. He was able to be successfully tapered off steroids without recurrence.

Conclusion: The coexistence of insulinoma with insulin antibodies is novel, and to our knowledge, has never been published.

Introduction

Insulinoma is the most common cause of hypoglycemia due to endogenous hyperinsulinemia and occurs in 1 to 4 people per million.[1] Insulin autoimmune syndrome (IAS), or Hirata's disease, is a rare syndrome of spontaneous hypoglycemia and antibodies against insulin. In Japan, IAS is the third leading cause of hypoglycemia, after insulinoma and extraintestinal neoplasia.[2] We present a novel case of a patient with an insulinoma and concomitant insulin antibodies.

Case Report

A 55-year-old male with medical history of hypertension, obstructive sleep apnea, and gastroesophageal reflux disorder was transferred to our center for evaluation of hypoglycemia. He was found unresponsive by a bystander who called emergency medical services. Past surgical, family, and social history were noncontributory. His vitals were a temperature of 36.8°C, blood pressure of 149/80 mm Hg, heart rate of 63 beats per minute, with a body mass index of 28 kg/m^2. On physical examination, he was diaphoretic with no other remarkable findings. Initial fingerstick blood glucose was 36 mg/dL (normal 74-99 mg/dL). After receiving oral glucose gel and 1 ampule of D50 (25 g glucose), his blood glucose level was 97 mg/dL (normal 74-99 mg/dL) with improved mentation. He revealed that he had initially started feeling sweaty, confused, and disoriented while he was driving. He pulled over and had lost consciousness by the side of the road where he was discovered by a bystander. He stated that he had 2 similar episodes before, both

Abbreviations: CT, computed tomography; IAS, insulin autoimmune syndrome; RFA, radiofrequency ablation.

* Address correspondence and reprint requests to Dr. David T. Broome, Department of Endocrinology, Diabetes & Metabolism, Cleveland Clinic Foundation, 9500 Euclid Avenue, F-20, Cleveland, OH 44195.
E-mail address: broomed@ccf.org (D.T. Broome).

https://doi.org/10.1016/j.aace.2021.01.009

within the past year, but had never lost consciousness. The first episode had resolved spontaneously while the second resolved once he had something to eat. He was admitted for a supervised 72-hour fast. Four hours into the fast, he began to develop neuroglycopenic symptoms (tremor, shaking, confusion), and his fingerstick glucose was 47 mg/dL (reference 74-99 mg/dL) with a concomitant serum glucose of 44 mg/dL (reference 74-99 mg/dL), C-peptide of 10.8 ng/mL (reference 0.5-2.7 ng/mL), insulin level of 106 microIU/mL (reference fasting levels <25 microIU/mL), and a proinsulin level of 675 pmol/mL (reference fasting levels <22 pmol/mL). His calculated insulin-to-C-peptide molar ratio was 0.20 (reference ratio is 1, <1 is suggestive of insulinoma).[3] However, he was also found to have a high insulin immunoglobulin G (IgG) antibody (predominantly proinsulin) titer of 2.4 U/mL (normal <0.4 U/mL) with a negative meglitinide and sulfonylurea screen. The patient was treated with 1 mg intravenous glucagon and his symptoms resolved with resolution of his hypoglycemia. A computed tomography (CT) of the abdomen/pelvis with contrast did not demonstrate a pancreatic mass, but an endoscopic ultrasound demonstrated a 16 x 11 mm mass in the pancreatic body that was biopsy-proven to be a neuroendocrine tumor. He was started on prednisone 20 mg twice daily as a means to reduce the antibody titers while he also underwent successful radiofrequency ablation (RFA) of the insulinoma. In follow-up, he was able to be tapered off steroids without recurrence of hypoglycemia. The coexistence of insulinoma with insulin antibodies is a novel finding that, to our knowledge, has never been published.

Discussion

Insulinoma is characterized by fasting hypoglycemia, although postprandial hypoglycemia can also be seen.[1] The diagnosis is established by demonstrating inappropriately high insulin levels during a spontaneous or induced (72-hour fast) hypoglycemic episode. Imaging is then used to localize the tumor (ultrasound, CT, magnetic resonance imaging, endoscopic ultrasound, or selective arterial calcium stimulation with hepatic venous sampling). Treatment options include surgical excision (partial pancreatectomy), enucleation, embolization, RFA, or cryotherapy.[1]

Insulin antibody syndrome is characterized by episodes of hyperinsulinemic hypoglycemia that most often occurs postprandially, although fasting- and exercise-induced hypoglycemia have been described. In Japan, it is associated with other autoimmune diseases in 96% of cases (Graves' disease, rheumatoid arthritis).[2,3] After a meal, there is initial hyperglycemia followed by hypoglycemia a few hours later. The hyperglycemia initially is due to a “tampon-like effect” where the anti-insulin antibodies bind to the insulin secreted in response to rising blood glucose levels after a meal.[2,3] This binding reduces insulin activity, resulting in hyperglycemia. As the blood glucose and insulin secretion declines, a “reservoir-like” effect kicks in and the insulin bound to the antibodies is released, resulting in hypoglycemia.[2,3] In cases of IAS, the insulin level is elevated, whereas the C-peptide level varies from very low in the fasting state to normal or raised postprandially. While pancreatic insulin and C-peptide are secreted in equimolar amounts, insulin binds to antibodies in patients with IAS. C-peptide continues to be metabolized at its normal rate with a half-life of 20 to 25 minutes. Thus, in a fasting state, C-peptide levels are low. The half-life of insulin, on the other hand, is variable in patients with IAS depending on its binding affinity to antibodies and the rate of association/dissociation.[4] The insulin/C-peptide molar ratio, hence, is usually >1 in IAS.[5] In contrast, insulin and C-peptide levels are both elevated in insulinoma, and the insulin/C-peptide molar ratio is usually <1 due to longer half-life of C-peptide. Treatment options for IAS include glucocorticoids, azathioprine, 6-mercaptopurine, plasmapheresis, and, more recently, rituximab.[6] Remission rate is ~80% after 3 to 6 months of treatment.[2]

Conclusion

It is important to distinguish between IAS and insulinoma due to different treatment approaches. The insulin/C-peptide molar ratio is >1 in IAS and is <1 in insulinoma.[5] In this case, his insulin level was 0.74 nmol/L with a C-peptide of 3.60 nmol/L. The insulin/C-peptide molar ratio was 0.20, suggestive of an insulinoma as the primary process rather than IAS. However, he also had a significant level of IgG insulin antibodies (predominantly directed at proinsulin), but it is unclear if he met full criteria for IAS.[7] IAS is a known autoimmune disorder that affects genetically predisposed individuals, and our patient did not have any other features suggestive of IAS.[7] It is hypothesized that the insulinoma led to high levels of circulating insulin, which in turn, stimulated the body to produce a high titer of insulin antibodies in response. Therefore, this patient had a mixed presentation of an insulinoma with coexisting insulin antibodies that responded well to both steroid treatment and RFA. He was successfully tapered off steroids and has been without recurrence of hypoglycemia.

Acknowledgment

Author Contributions

A.I. and D.T.B. wrote the manuscript. V.M. and D.Y. edited and revised the manuscript.

Disclosure

The authors have no multiplicity of interest to disclose. The authors received no specific funding from public or private sectors for this work.

References

1. Okabayashi T, Shima T, Sumiyoshi T, et al. Diagnosis and management of insulinoma. *World J Gastroenterol*. 2013;19(6):829–837.
2. Lupsa B.C., Chong A.Y., Cochran E.K., Soos M.A., Semple R.K., Gorden P., Autoimmune forms of hypoglycemia. *Medicine (Baltimore)*. **88** (3):141-153
3. Hu X, Chen F. Exogenous insulin antibody syndrome (EIAS): a clinical syndrome associated with insulin antibodies induced by exogenous insulin in diabetic patients. *Endocr Connect*. 2018;7(1):R47–R55.
4. Schlemper RJ, Uchigata Y, Frölich M, Vingerhoeds AC, Meinders AE. Recurrent hypoglycaemia caused by the insulin autoimmune syndrome: the first Dutch case. *Neth J Med*. 1996;48(5):188–192.
5. Censi S, Mian C, Betterle C. Insulin autoimmune syndrome: from diagnosis to clinical management. *Ann Transl Med*. 2018;6(17):335.
6. Saxon DR, McDermott MT, Michels AW. Novel management of insulin autoimmune syndrome with rituximab and continuous glucose monitoring. *J Clin Endocrinol Metab*. 2016;101(5):1931–1934.
7. Ismail A. The insulin autoimmune syndrome (IAS) as a cause of hypoglycaemia: an update on the pathophysiology, biochemical investigations and diagnosis. *Clin Chem Lab Med*. 2016;54(11):1715–1724.