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Insulin autoimmune syndrome associated with the use of thiocolchicoside: A Case report

Tiyokolşikosid kullanımı ile ilişkili insülin otoimmün sendromu: Bir olgu Sunumu

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SUMMARY

Insulin autoimmune syndrome (IAS) is a disease characterized by hypoglycemia and insulin antibodies without insulin usage. We report the case of a patient diagnosed with IAS that was associated with the use of thiocolchicoside. A 62-year-old female patient was admitted to our clinic with fasting and postprandial hypoglycemia symptoms. She had a fasting glucose level of 47mg/dl, and high insulin, C-peptide and insulin antibody levels were detected. However, she had no signs of hypoglycemia during a 72 hour fasting test. In addition, the patient had used thiocolchicoside for a week a month prior to the beginning of her symptoms, but she was not taking any insulin or diabetic medications. A diagnosis of IAS was made, and the patient was put on an appropriate diet. Three months following this diagnosis, the patient's complaints have minimilized, and the insulin and C-peptide levels have decreased.

Keywords: Insulin autoimmune syndrome, hypoglycemia, thiocolchicoside

ÖZET

İnsülin otoimmun sendromu (IAS) hipoglisemi ve insülin kullanmaksızın insülin antikorlarının varlığı ile karakterize nadir bir hastalıktır. Biz tiyokolşikosid kullanımına bağlı IAS tanısı koyduğumuz bir vakayı sunuyoruz. 62 yaşında bayan hasta açlıkta ve postprandial hipoglisemi semptomları ile başvurdu. Açlık kan şekeri 47mg/dl ve insülin, C peptid, insülin antikor düzeyi yüksek olarak tesbit edildi. 72 saat uzamış açlık testinde hipoglisemi yaşamadı. Şikayetlerinin başlamasından bir ay öncesinde bir hafta süreyle tiyokolşikosid kullanımı vardı, insülin ve diyabetik ilaç kullanımı yoktu. Hastaya insülin otoimmun sendromu tanısı kondu ve diyet tedavisi önerildi. Hastanın üç ay sonrasında şikayetleri azaldı insülin ve C peptid düzeyi düştü.

Anahtar sözcükler: İnsülin otoimmun sendromu, hipoglisemi, tiyokolşikosid

INTRODUCTION

The first case of insulin autoimmune syndrome (IAS) was reported in 1970 by Hirata et al.[1]. and it is characterized by frequent hypoglycemic attacks associated with the presence of autoantibodies to insulin in patients who have not received insulin injections[2]. Insulin-binding antibodies routinely develop in patients with diabetes who are treated with insulin, but they develop spontaneously in patients with IAS. In the former condition, the functional significance of the antibodies is unknown, whereas with IAS, a high titer of low-affinity polyclonal antibodies may cause glucose intolerance along with episodes of hypoglycemia as a result of the intermittent and unpredictable release of bound insülin[3]. Underlying autoimmune disorders or exposure to specific drugs, especially those containing sulfhydryl groups, have been presumed to be responsible for the development of IAS[4]. Thiocolchicoside is a frequently used sulfhydryl-baring muscle relaxant. Our study is significant in that it presents the first case of IAS associated with the use of thiocolchicoside.

CASE REPORT

A 62-year-old female was admitted to our clinic with complaints of sweating, palpitation, fatigue, a sense of hunger after fasting and during postprandial periods that had persisted for a month. The patient's fasting glucose level was 47mg/dl while the insulin and C-peptide levels were 2600µIU/mL (2.6-24.9) and 10.90 ng/ml (0.9-7.1), respectively. She had completed a 72-hour fasting test, but had no signs of hypoglycemia afterwards as the lowest glucose level was 66 mg/dl while the insulin and C-peptide levels were 2580 µIU/mL (2.6-24.9) and 10.60 ng/ml (0.9-7.1), respectively. In addition, abdominal ultrasound and computed tomography (CT) showed that the pancreas was normal. A 75g oral glucose tolerence test was performed, and measurements were taken at initiation (77 mg/dl) and at the first hour (168mg/dl), second hour (211mg/dl), third hour (177mg/dl) and fourth hour (96mg/dl). Additionally, the glycated hemoglobin (HbA1c) rate was 6.2%. These test results revealed that the patient had diabetes mellitus (DM) but no reactive hypoglycemia. Furthermore, the thyroid function tests were normal, and other parameters yielded the following results: anti-thyroid peroxicase (anti-TPO) antibody: 6.2 IU/ml(0-34), anti-triglobulin antibody:10.612IU/ml(0-115), sedimentation: 25mm/h, and hemoglobin: 12.2g/dl. The patient also tested negative for the following: antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), antimitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), and anti-citrullinated protein antibody (anti CCP). In addition, the rate of insulin antibodies was 83% (< 8.2). The patient's history included the use of thiocolchicoside for a week due to muscle pain a month before the onset of her complaints but no use of insulin or diabetic medications. The patient was then diagnosed with IAS and put on an appropriate diet. After three months, the patient's complaints were minimilized, and the insulin and C-peptide levels had decreased to 980 µIU/mL (2.6-24.9) and 7.20ng/ml (0.9-7.1), respectively.

DISCUSSION

Hyperinsulinemic hypoglycemia can occur because of drugs, critical illness, hormonal deficiencies, non-beta (ß) cell tumors, endogenous hyperinsulinism (including insulinoma, the autoimmune process, etc.), or metabolic disorders in infancy and childhood. Underlying autoimmune disorders or exposure to specific drugs were presumed to be responsible for the development of IAS. Some medications, such as sulfydryl medications (e.g., methimazole, alphamercaptopropionyl glycine, and gluthatione), hydralazine, isoniazide, procainamide, and penicillin, have also been reported to trigger autoantibody production related to this syndrome[4]. Additionally, frequently usage of alpha (α)-lipoic acid have been increasingly held responsible for IAS development[5]. In most cases, insulin autoantibodies appear a few weeks after beginning treatment, with a drug containing the sulphydryl group[2]. Moreover, on rare occasions, IAS may also result from monoclonal insulin-binding autoantibodies produced by multiple

myeloma or benign monoclonal gammopathy[4].

Our patient received one of the sulfydryl medications, thiocolchicoside, a month prior to her complaints of spontaneous hypoglycemia. In addition, she had increased insulin autoantibody, insulin, and C-peptide levels. All of these factors led to the diagnosis of IAS. The patient also tested negative for autoantibodies related to autoimmune diseases, and multiple myeloma was not a viable option based on the clinical findings. We also considered the possibility of insulinoma since it is the most prevalent cause of hypoglycemia, but the diagnostic results did not point to this type of tumor. In addition, the ultrasonography (USG) and computed tomography (CT) results were normal, and hypoglycemia was not observed during the 72-hour fasting test.

Insulin autoimmune syndrome is a very rare condition that is associated with a strong genetic predisposition. Since Hirata[1] reported the first case of IAS in 1970, the majority of cases have been Japanese, with only a few cases having been reported among Caucasians and other non-Oriental ethnic groups[4]. Uchigata et al. showed that the HLA-DR4 allele, DRB1*0406, is associated with an increased susceptibility to IAS among the Japanese[6], and a strong correlation exists between HLA-DRB1*0406 and IAS[2]. Hence, the extremely low prevalence of IAS among Caucasians can be explained by the low prevalence of DRB1*0406 in that population[4]. However, we did not perform a genetic analysis on our patient.

Our patient exhibited a diabetic response on a 75 g oral glucose tolerance test, suggesting that the insulin secreted in response to the increased blood glucose levels following the glucose load became bound to antibodies. Consequently, this impaired its effects, despite the excessive amount of insulin that was secreted. Our patient also had a high C-peptide level, suggesting that her pancreatic β cells may also have been overstimulated after eating the carbohydrate-rich food in her special prescribed diet, which can also lead to obesity, as seen in patients with insulinoma[7]. Therefore, care should be taken when formulating the contents of a supplementary diet.

In the majority of the Japanese patients with IAS, no treatment was required, and spontaneous remission occured within six months of onset. However, in cases of prolonged hypoglycemia or when IAS is severe, treatment via plasmapheresis, immunosuppressive medication, or glucagon injections may be undertaken[4]. In our case, three months following this diagnosis complaints of the patient have minimilized, and the insulin and C-peptide levels have decreased with no specific treatment except special regulated diet.

CONCLUSION

Insulin autoimmune syndrome must be considered in the differential diagnosis of hyperinsulinemic hypoglycemia in order to avoid undue pancreatic surgery, especially in patients taking drugs known to be associated with this syndrome. Our study involved the first case of patient being diagnosed with IAS in association with the use of thiocolchicoside. However, no serious hypoglycemia was seen in spite of high insulin, C-peptide, and insulin antibody levels, which was clinically significant. In addition, to the best of our knowledge, this is most likely the first case of IAS in a Turkish patient.

REFERENCES

1. Hirata Y, Ishizu H, Ouchi N, et al. Insulin autoimmunity in a case with spontaneous hypoglycemia. J Jpn Diabetes Soc 1970; 13: 312-320.

2. Takeuchi Y, Miyamoto T, Kakizawa T, Shigematsu S, Hashizume K. Insulin Autoimmune Syndrome possibly caused by alpha lipoic acid. Intern Med 2007; 46: 237-9.

3. Waldron-Lynch F, Inzucchi SE, Menard L, et al. Relapsing and remitting severe hypoglycemia due to a monoclonal anti-insulin antibody heralding a case of multiple myeloma. J Clin Endocrinol Metab 2012; 97: 4317-23.

4. Masjhur JS. Insulin Autoimmune Syndrome (Hirata's disease): severe hypoglycemic episodes in Graves' hyperthyroidism patient treated with methimazole. Acta Med Indones 2005; 37: 214-7.

5. Uchigata Y. The novel agent, alpha lipoic acid, can cause the development of insulin autoimmune syndrome. Intern Med 2007; 46: 1321-2.

6. Uchigata Y, Hirata Y, Omori Y, Iwamoto Y, and Tokunaga K. Worldwide differences in the incidence of insulin autoimmune syndrome (Hirata's disease) with respect to the evolution of HLA-DR4 alleles. Human Immunol 2000; 61:154-7.

7. Deguchi A, Okauchi Y, Suehara S, Mineo I. Insulin autoimmune syndrome in a health supplement user: the effectiveness of cornstarch therapy for treating hypoglycemia. Intern Med 2013; 52: 369-72.