Case Report

Reversible adrenal insufficiency and heterophile antibodies in a case of autoimmune polyendocrinopathy syndrome

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ABSTRACT

A 27-year-old male was admitted with diabetic ketoacidosis and altered sensorium with slurring of speech and ataxia. He was managed with intravenous insulin and fluids and later shifted to basal bolus insulin regimen and during further evaluation was diagnosed to be suffering from primary hypothyroidism and adrenal insufficiency. He was started on thyroxin replacement and steroids only during stress. After three months of follow up he was clinically euthyroid. His glycemic control was adequate on oral anti-hyperglycemic drugs and adrenal insufficiency recovered. However, his thyrotropin levels were persistently elevated on adequate replacement doses of thyroxin. His repeat TSH was estimated after precipitating serum with polyethylene glycol which revealed normal TSH. Here we report reversible adrenal insufficiency with hypothyroidism with falsely raised TSH because of presence of heterophile antibodies in a case of poly glandular endocrinopathy syndrome.

Key words: Adrenal insufficiency, autoimmune polyendocrinopathy syndrome, heterophile antibody, primary hypothyroidism, type-1 diabetes mellitus

Introduction

Autoimmune disorders are among the most common disorders in endocrinal disease, and may coexist with other organ-specific autoantibodies.[1] Hypothyroidism is a clinical syndrome resulting from the deficiency of thyroid hormones, which in turn results in a generalized slowing down of metabolic processes. Thyroid hormones exert direct cellular effects on almost all tissues of the body and deficiency leads to multi organ dysfunctions which are reversible after thyroxin replacement therapy i.e., renal and hepatic dysfunction.[2] Abnormalities in endocrine function have also been reported in primary hypothyroidism, which can be due to deficiency of thyroid hormone *per se* or associated with polyglandular autoimmune endocrinopathies.[2] Here we report a case of autoimmune thyroiditis with type-1 diabetes mellitus (T1DM), who presented with diabetic ketoacidosis and inadequate cortisol response to adrenocorticotropin hormone (ACTH) stimulation test. After thyroxin replacement his glycemic control was adequate with oral anti-hyperglycemic drugs (OADs) and cortisol response to ACTH normalised. He had discordantly elevated thyrotropin (TSH) with normal T3 and T4 levels and clinical euthyroidism on adequate thyroxin replacement. Spuriously high TSH in assay can be due to heterophillic antibodies,[3] anti-TSH antibodies[4] or macro-TSH.[5] In our case discordant result were found to be due to heterophile antibody.

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Case Report

A 27-year-old male presented in emergency with history of fever of twodays duration which was moderate grade, intermittent associated with chills followed by alteration in sensorium and vomiting. At admission, he

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was detected to have hyperglycemia (Random plasma Glucose-635 mg/dl); urine ketones were positive; pH-7.16; bicarbonate-8 meq/L; serum sodium-123 meq/L serum potassium-5.4 meq/L; glycated hemoglobin (A1C)-10.4%. He was managed with intravenous insulin and fluids with improvement in clinical status. There was no family history of any autoimmune and endocrine illness. After improvement, examination revealed normal body mass index (BMI-21.5 kg/m^2) and slurring of speech with ataxia. His MRI brain was normal. Thyroid function test revealed elevated TSH (85 μIU/mL; normal 05-6.5) with low total T3 (0.45 ng/ml; normal 0.8-2.1) and low total T4 (2.01 μg/dl; normal 5.5-13.5). He was positive for anti-thyroid peroxidase and anti-glutamic acid decarboxylase (anti-GAD) antibodies. In view of autoimmune thyroid disease and T1DM, he was evaluated for presence of polyglandular endocrinopathies. He had subnormal response to ACTH stimulation test (S. cortisol basal-7.9 μg/dl, post ACTH cortisol-13.69 μg/dl) with elevated basal serum ACTH (94 pg/ml, normal 15-57). He had normal gonadotropin and testosterone levels. Anti-tissue transglutaminase antibody titres were normal. He was stabilized on basal-bolus insulin regimen and started on thyroxin replacement therapy. In view of small requirement of insulin doses, he was switched to OADs (glimepiride and metformin) and later continued only on metformin. He had no gastrointestinal symptoms, his blood pressure was normal, imaging of pituitary (MRI) and adrenal (CT) was normal; hence steroid replacement was withheld, and only stress dosing was advised. At three months follow up, he had achieved adequate glycemic control with OADs (A1C-6.7%); had normal cortisol response to ACTH (S. Cortisol basal/ACTH stimulated-6.57/19.93 μg/dl). However, thyroid function test revealed normal total T3 (1.7 ng/ml) and total T4 (7.4 μg/dl) and elevated TSH (55.2 μIU/ml), while he was clinically euthyroid and his slurring of speech and ataxia had recovered completely. TSH was persistently measured high on repeated assays. In view of markedly raised TSH with normal T3, T4 with compliance to treatment and clinically euthyroid state, his serum was precipitated with polyethylene glycol (PEG) and repeat thyroid profile revealed normal TSH (0.7 μIU/ml) indicating presence of heterophile antibodies.

Discussion

Autoimmune polyendocrinopathy syndromes (APS) are monogenic or polygenic clinical syndromes of multiple endocrinopathies with presence of autoimmunity as indicated by positive autoimmune markers. APS-1 is monogenic form characterized by presence of candidiasis, autoimmune Addison's disease and autoimmune hypoparathyroidism usually presenting during first decade of life. APS-2 is defined by presence of autoimmune adrenal insufficiency with presence of either autoimmune thyroid disease or autoimmune T1DM. Another entity is incomplete APS-2 which is characterized by presence of autoantibodies to adrenal, thyroid, or pancreatic islet cell with normal function and one clinically evident endocrinopathy. APS-3 is occurrence of autoimmune thyroid disease with autoimmune DM and absence of autoimmune adrenal insufficiency. APS-4 is characterized by presence of multiple autoimmune endocrinopathies which does not fall into APS1-3.[1]

Our case had evidence of T1DM as presentation was with diabetic ketoacidosis and anti-GAD antibodies were positive; however, during follow up his glycemic control could be achieved with OADs. Many individuals with latent autoimmune diabetes of adult (LADA) may be controlled by OADs, though they may require insulin early and have late age of onset of autoimmune diabetes.[6] Moreover, GAD antibodies have been found to have limited value in predicting insulin requirement in UKPDS.[7] There is impairment of insulin secretion in GAD positive subjects with Hashimoto's thyroiditis compared to those without thyroid autoimmunity, which could have precipitated ketoacidosis.[8] With thyroxin replacement his beta cell function might have recovered and glycemic control could be achieved with OADs. Another possibility is a well-known phenomenon of honey moon phase of T1DM, which is defined as the phase when calculated insulin dose-adjusted HbA1c [A1c(%) +(4 × insulin dose (U/kg/hr)][9] is below 9%. In our patient insulin requirement has disappeared. In view of normal BMI, absence of family history, late age of onset he could be classified as LADA in whom diabetic ketoacidosis was precipitated by acute stress.

He also had autoimmune thyroiditis with primary hypothyroidism. After thyroxin replacement he became clinically euthyroid but his hormonal profile showed elevated TSH levels. Discordantly elevated TSH can be due to heterophillic antibodies,[3] anti-TSH antibodies[4] or macro-TSH.[5] Heterophile antibodies are antibodies induced by external antigens (heterophile antigens) that cross-react with self-antigens. The clinical importance of these antibodies is that, the presence of these antibodies in the serum of the individual interacts with immunometric assays and produce false high or false low values. There are two types of heterophile antibodies, the bridging antibodies and the blocking antibodies; the former produces false high values and the later false low values.[10] These heterophile antibodies can be removed from the test serum by treating the serum with PEG which precipitates antibodies in the serum, by heterophile blocking tubes[5] or using single chain antibodies.[11] These antibodies can also be assessed with serial dilution with non-linear recovery, measuring biological activity

in bioassay system and gel filtration chromatography.[5] The most common interferences are with TSH, LH and FSH but any hormone can be affected by presence of heterophile antibodies. Hence, presence of heterophile antibodies was suspected and was confirmed on repeat test after polyethylene glycol precipitation, which revealed normal TSH levels. In clinical practice overzealous reliance on normalizing TSH values in such patients, may wrongly lead to over replacement of thyroxin and unwanted side effects.

Among T1DM patients up to 15-30% patients develop autoimmune thyroid disease and about 0.5% have adrenal insufficiency.[1] This co-occurrence of T1DM and autoimmune thyroid disease is due to sharing of same autoimmune susceptibility genes like HLA-DR, CTLA-4, PTPN22. Our patient also had evidence of asymptomatic adrenal insufficiency. However, adrenal antibodies could not be tested due to non-availability. Two cases of asymptomatic adrenal insufficiency have been reported in patients with autoimmune thyroiditis who were negative for adrenal antibodies.[12] Surprisingly, his adrenal function recovered after achieving euthyroidism with thyroxin replacement, which to best of our knowledge, has not been reported in the literature, though, vice versa has been reported.[13] Hypothyroidism is a state of altered metabolic dysfunction which is characterized by reversible alterations of lipid profile, uric acid, blood pressure, liver and renal function. Hypothalamo-pituitary-adrenal axis is suppressed in hypothyroidism which is proportional to severity of hypothyroidism.[14] Hence, it can be hypothesized that our patient may had subclinical adrenal dysfunction due to adrenal autoimmunity which in presence of lazy pituitary due to primary hypothyroidism and acute stress due to DKA, caused adrenal insufficiency. On recovery of hypothalamo-pituitary-adrenal axis caused by stress and normalization of thyroid function his adrenal was able to respond to ACTH stimulation. Isolated corticotrophin deficiency has also been described in patient with APS-3,[15,16] but ACTH levels were elevated in our patient excluding this possibility. Asymptomatic subclinical adrenal insufficiency has also been reported in 25% of type-1 DM patients; however, reversibility has not been reported.[17] Early adrenal hypofunction without clinical adrenal insufficiency can be detected be ovine CRH test in patients with normal cortisol response to ACTH stimulation test; however, this could not be performed.[18]

Our patient's autoimmune work up for anti-21 hydroxylase, anti-insulin, and anti-ZnT8 antibodies could not be tested because of cost limitations and limited availability. In view of recovered adrenal function and lack of measurement of adrenal antibodies, we made provisional diagnosis of APS-3, and he is planned for regular follow up for adrenal function later during course of illness.

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