CLINICAL VIGNETTE

Suspected Type 2 Polyglandular Syndrome

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A 26-year-old female was referred to Endocrine for evaluation and management of type 1 diabetes. She was followed by Gynecology for amenorrhea and infertility. They noted an A1c of 12.9% and positive islet cell antibody, prompting referral. Since her diagnosis of diabetes, she adopted a low-carbohydrate diet plan and maintained a vigorous and active lifestyle, including surfing, yoga, running, CrossFit, and hiking. Her father was diagnosed with type 1 diabetes at the age of 40. Review of systems, revealed no menstrual period in 6 months, and a 10 lb weight loss. She denied cold intolerance, fatigue, and GI/GU symptoms. She was well-appearing with a BMI 22 kg/m2, and her physical exam was unremarkable.

Laboratory evaluation included positive glutamic acid decarboxylase-65 antibodies, positive ICA-512 auto antibodies, low to undetectable C-peptide, positive thyroid peroxidase antibody (TPO), and positive 21-hydroxylase antibody. Celiac antibody panel was weakly positive. Thyroid tests, complete blood count, and comprehensive metabolic panel were unremarkable. DHEA-sulfate, LH, FSH, estradiol, progesterone, 17 alpha hydroxyprogesterone, and anti-mullerian hormone levels were within normal limits. Cosyntropin stimulation testing was normal at >18 mcg/dl.

She started continuous monitoring and maintained glucose in target range (70-180 mg/dl) at least 90% of the time. This was achieved with minimal insulin of only 10 units of basal insulin each day with infrequent prandial insulin. She started on levothyroxine 25mcg daily given potential correlation of Hashimoto's thyroiditis and miscarriage. She was evaluated by reproductive endocrinology, and further testing demonstrated hypothalamic amenorrhea. With liberation of caloric intake, her menstruation returned.

Discussion

Polyglandular autoimmune syndromes (PAS) are complex, heterogeneous diseases characterized by autoimmune dysfunction that affect both endocrine and non-endocrine organs. The most common in adults is polyglandular autoimmune syndrome type 2 (PAS-2), which often presents with primary adrenal insufficiency, autoimmune thyroid disease, and type 1 diabetes. PAS-2 has multifactorial polygenetic inheritance and has been associated with human leukocyte antigens (HLA) DR3, DR4, DQ2, DQ8 as well as non-HLA genes such as CTLA-4 and PTPN22.[1] Prevalence ranges from 1.4 to 2 per 100,000 in the general population.[2] Average age of diagnosis is between 20-40 years and it is three times more common in women.[3]

In PAS-2, the presence of autoantibodies lead to lymphocytic infiltration causing organ-specific damage.[1] Primary adrenal insufficiency is the principal manifestation and is the initial presentation in approximately 50 percent of patients.[4] Autoimmune thyroid disease can manifest as either chronic autoimmune thyroiditis or Graves' disease. Type 1 diabetes occurs in around 50 percent of patients.[4] Additional autoimmune manifestations which may occur include: celiac disease, myasthenia gravis, alopecia, vitiligo, pernicious anemia, premature ovarian insufficiency, thrombocytopenic purpura, Sjogren's syndrome rheumatoid arthritis, and primary antiphospholipid syndrome.[1,5]

Symptoms vary depending on the initial presenting diseases process. Patients may present with vague symptoms of weight loss, fatigue, anorexia, generalized weakness. Patients with primary adrenal insufficiency may have mucosal and cutaneous hyperpigmentation, orthostatic hypotension, and low blood glucose levels. Type 1 diabetes patients can present with polyuria, polydipsia, and hyperglycemia. Thyroid symptoms will vary depending on whether they present with hypothyroidism or hyperthyroidism.

Diagnosis of patients with PAS-2 is made by documenting at least 2 out of 3 manifestations including primary adrenal insufficiency, autoimmune thyroid disease, and type 1 diabetes mellitus. Diagnosis is often delayed due to rarity of disease and nonspecific clinical manifestations. Organ-specific antibodies such as 21-hydroxylase antibody for Addison's disease, GAD-65 and ICA-512 for type 1 diabetes, and TPO antibody for autoimmune thyroid disease can be helpful in establishing a diagnosis. However, the presence of these antibodies does not predict glandular failure.[1] Management of PAS-2 focuses on hormonal replacement therapy as needed. Patients with PAS-2 and their family members should be monitored regularly due to future risk of developing organ-specific dysfunction.

Our patient had multiple positive antibody levels concerning for PAS-2 diagnosis, although at this time, she does not fully meet criteria for diagnosis. She has no adrenal disease. Although she has positive TPO antibodies suggestive of Hashimoto's thyroiditis, she is clinically euthyroid and her TSH remains within normal limits. Positive TPO antibodies have been strongly associated with miscarriage. She does not have a history of miscarriage, though is interested in getting pregnant. Levothyroxine may provide some benefit though statistical improvement in the rates of live births has not been established.[6] Interestingly, patients with PAS-2 often have

premature ovarian failure, however her evaluation was consistent with hypothalamic amenorrhea, with return of menstruation after liberation of caloric intake. We plan to continue yearly monitoring of thyroid labs, cosyntropin stimulation test, and continued support for her desire for pregnancy.

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