EJCRIM
European Journal
of Case Reports
in Internal Medicine

A SILENT CAUSE OF SHOCK: AUTOIMMUNE POLYGLANDULAR SYNDROMES

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Received: 11/05/2024 **Accepted:** 13/05/2024 **Published:** 27/05/2024

Conflicts of Interests: Each author certifies that he/she, a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript. The authors have not used generative artificial intelligence or artificial intelligence associated technologies.
Patient Consent: Consent has been obtained from the patient and he/she certifies the use of their clinical information.
Acknowledgments: We would like to thank the teaching staff for affording us the opportunity to learn from clinical cases.

How to cite this article: Colantonio MA, Hartzell M, Shannon B, Iyer A. A silent cause of shock: autoimmune polyglandular syndromes. *EJCRIM* 2024;**11**:doi:10.12890/2024_004627

ABSTRACT

Addison's disease is a rare, autoimmune condition leading to destruction of the adrenal gland. Autoimmune conditions are known to commonly co-occur. When Addison's disease presents in the setting of autoimmune thyroid disease and/or type 1 diabetes, this condition is termed autoimmune polyendocrine syndrome type II, a rare endocrinopathy found in roughly 1.4-4.5 per 100,000 individuals. Here, we describe a clinical case presenting with hypotension refractory to fluid resuscitation and electrolyte derangements later diagnosed as autoimmune polyendocrine syndrome type II.

KEYWORDS

Adrenal insufficiency, Addison's disease, Hashimoto's disease, autoimmune polyglandular syndromes, autoimmune polyendocrine syndrome type 2

LEARNING POINTS

- Primary adrenal insufficiency may present clinically as shock refractory to fluid resuscitation.
- Autoimmune polyglandular syndrome type 2 is a rare autoimmune condition occurring in 1.5-4.5 per 100,000 individuals.
- The presence of an underlying autoimmune condition should raise suspicion for multiple concurrent autoimmune conditions.

INTRODUCTION

Autoimmune diseases (AD) are chronic pathologies defined by the body's loss of tolerance to self-antigens which can ultimately lead to systemic and/or organ dysfunction[1]. AD's often manifest in multi-organ dysfunction which can include endocrinopathies[1]. As an important regulator in the production of essential endocrine hormones, the adrenal gland is responsible for producing glucocorticoids, mineralocorticoids, and androgens[2]. Adrenal insufficiency (AI) is a disorder characterized by the diminished production of these hormones and can be categorized into three different groups: primary, secondary, and tertiary adrenal insufficiency[2]. Several etiologies have been found for primary AI, including various medications and infections. However,

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the most important cause of primary AI is secondary to autoimmune destruction of the adrenal gland, specifically termed Addison's disease[2]. 90% of cases of Addison's disease is caused by autoimmune antibodies targeting the 21-hydroxylase enzyme and affects about 1 in 20,000 individuals[2,3]. Individuals at high risk for development of primary AI include those harboring the HLA-B8, HLA-DR3-DQ2 and HLA-DR4-DQ8 alleles, respectively[3]. Early diagnosis of AI is critical as progression to fulminant adrenal crisis can be life-threatening, with possible complications such as severe hypoglycemia, shock and even death[4].

Clinical presentation of AI varies significantly, with symptoms ranging from nausea, vomiting, hypotension, abdominal pain, and weight loss. Clinical signs shown to be most frequently associated with AI include weakness, anorexia, weight loss and electrolyte disturbances[5]. However, the diagnosis of AI cannot be ruled in or out based on these signs alone[5]. If there is a high clinical suspicion for AI, an 8 AM cortisol level should be obtained, as multiple retrospective studies have established this as a reliable method for screening individuals suspected of AI[6]. An 8 AM cortisol of <3 mcg/dl makes AI very likely, whereas a level between 3 and 18 mcg/dL is indeterminate and requires further workup with an adrenocorticotropin hormone (ACTH) stimulation test[7,8]. After confirming the diagnosis, glucocorticoid therapy should be initiated with hydrocortisone historically used as the preferred agent[9]. In the setting of hemodynamic instability with concerns for underlying adrenal crisis, stress dose hydrocortisone should be initiated at 50 mg four times daily until the patient regains clinical stability. After this glucocorticoid are preferably tapered until a maintenance dose of 15 to 25 mg daily is achieved[10]. Fludrocortisone can also be added and should be considered to supplement mineralocorticoid activity.

In the setting of a newly diagnosed autoimmune disease, patients should be screened for other underlying autoimmune pathologies. When multiple, specific autoimmune conditions are found to co-exist, some can be further classified[11]. Autoimmune polyglandular syndromes (APS) were first described in 1980 and were further classified into four distinct subgroups[11]. Autoimmune polyendocrine syndrome type II (APS type 2), characterized as Addison's disease in combination with thyroid autoimmune disease and/or type 1 diabetes mellitus is a rare pathology found in about 1.4-4.5 per 100,000 individuals. Here, we describe a diagnosis of APS type 2 in a patient with newly diagnosed Addison's disease in the setting of underlying Hashimoto's hypothyroid disease.

CASE DESCRIPTION

A 43-year-old female with past medical history of hypothyroidism initially presented to the emergency department of our academic medical center with a chief complaint of nausea. Upon presentation, the patient reported weakness, muscle stiffness, low blood pressure, nausea and vomiting for the past 7-10 days. The patient also reported an unintentional 4 kg weight loss over the past week and an unintentional 9 kg weight loss for the last 6 months. She was hypotensive on admission with a blood pressure of 88/48 mmHg with other vital signs within normal limits. In the emergency department, laboratory workup was significant for thyroid stimulating hormone (TSH) of 28.5 µIU/ml and free T4 levels of 0.64 µIU/ml. Her electrolyte panel revealed a sodium of 124 mmol/l, chloride 92 mmol/l and calcium of 10.9 mmol/l. A mild acute kidney injury was also noted with a level creatinine of 1.48 mg/dl. Computed tomography scan of the chest abdomen and pelvis was largely unremarkable for acute pathology. The patient was admitted to the medicine service for further workup of her persistent hypotension, weight loss and electrolyte abnormalities. Upon chart review and further interview of the patient, the patient noted she had a prior diagnosis of invasive squamous cell carcinoma and immature ovarian teratoma about 10 years ago during a prior pregnancy. At that time, the patient underwent an emergent right salpingo-oophorectomy during her pregnancy. However, due to the size of the mass, the mass was removed through the abdominal wall and contents were aspirated.

Due to the persistent hypotension, the patient was given 2 liters of intravenous (IV) fluids with PlasmaLyte in the emergency department. The patient's blood pressure mildly improved with fluid resuscitation. Due to the patient's persistent hypotension and electrolyte abnormalities including hyponatremia at admission, at 8:00 AM a cortisol level was obtained due to a suspicion for adrenal insufficiency. Further evaluation revealed a cortisol level less than 1 µg/dl, making adrenal insufficiency likely. Anti-thyroid peroxidase (Anti-TPO) antibodies were also obtained due to persistent, uncontrolled hypothyroidism. Results were positive for antibodies to anti-TPO, confirming the etiology of her long-standing hypothyroidism as secondary to Hashimoto's disease. Endocrinology was consulted for further management. Per their recommendations, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-S), 21-hydroxylase antibodies, a renin to aldosterone ratio and an antibody screen for type 1 diabetes were ordered. Stress dose steroids dosed at 50 mg hydrocortisone q.6 hours for 1 day were initiated and tapered to15 mg q.a.m. and 5 mg q.p.m. through hospitalization and at discharge. The patient's blood pressure improved after initiation of hydrocortisone. Further workup of likely primary adrenal insufficiency revealed positive antibodies to 21-hydroxylase confirming the etiology of primary autoimmune adrenal insufficiency. Antibody screen for type 1 diabetes mellitus with GAD65, islet cell antibodies and zinc transporter antibodies were negative. Follicular stimulating hormone (FSH) levels were also obtained to screen for ovarian insufficiency as the patient endorsed no longer having menstrual cycles at admission. FSH levels were found to be 10.3 mIU/dl, concerning for primary insufficiency. The patient's hypercalcemia ultimately improved with initiation of IV fluids. Due to the patient's

history of invasive squamous cell carcinoma in the setting of a high-grade lesion within and immature teratoma, a pelvic ultrasound was performed which revealed redemonstration of a simple cyst adjacent to the left ovary measuring 2.7 cm, which may represent a para-ovarian cyst. This cyst was thought to be benign due to an O-RADS score of 2. Prior to discharge, the patient's Synthroid was increased to 100 mcg daily. The patient clinically did well after discharge and remained free of any symptoms of adrenal insufficiency. She was referred for close follow-up with endocrinology as an outpatient.

DISCUSSION

Autoimmune conditions are relatively common, with a prevalence of about 3,000 per 100,000 individuals[1]. It is important for clinicians to recognize these disease-states early in their clinical course as they can lead to significant morbidity and mortality[1]. Here, we described a rare diagnosis of primary adrenal insufficiency with an initial presentation of unintentional weight loss, nausea, vomiting, hypotension, and muscle weakness. These presenting symptoms in this case were similar to common associated symptoms with AI, as noted above[1]. When AI is suspected and later confirmed, it is essential to start treatment promptly. Multiple studies have validated hydrocortisone as the primary treatment of choice, especially in those with signs of impending adrenal crisis[12]. In patients with development of acute adrenal crisis, studies have indicated that continuous infusion of hydrocortisone is likely superior to intermittent bolus of hydrocortisone[12]. Alternative therapies to hydrocortisone include prednisolone, methylprednisolone, and dexamethasone[12]. In cases where infection is the suspected cause, antibiotics may be warranted[12]. Our patient had significant clinical improvement with administration of stress-dose hydrocortisone with the eventual transition to once daily dosing at much lower doses.

Once AI is suspected, further workup must be pursued to accurately determine the etiology of AI, which can be categorized into three different classes: primary, secondary, and tertiary AI[2]. Primary AI is due to dysfunction at the level of the adrenal gland, whereas secondary AI is due to deficient ACTH release from the pituitary gland and tertiary AI due to insufficient corticotrophin releasing hormone (CRH) from the hypothalamus[2]. Once suspicion of AI was heightened with an 8:00 AM cortisol level less than 1 ug/dl, antibodies to 21-hydroxylase, DHEA-S and a renin to aldosterone ratio were ordered. Results revealed positive antibodies to 21-hydroxylase, confirming the diagnosis of autoimmune AI due to Addison's disease. Further workup of the patient's underlying hypothyroidism revealed positive anti-thyroid peroxidase antibodies, confirming the diagnosis of Hashimoto's hypothyroid disease. Together, these two diagnoses further characterize APS type 2, a rare endocrinopathy occurring in roughly 1.4 to 2 per 100,000 individuals[13]. The diagnosis of APS type 2 requires autoimmune AI along with either autoimmune thyroid disease or type 1 autoimmune diabetes mellitus[13]. Our case demonstrated and fulfilled this criterion by the presence of antibodies to 21-hydroxylase and anti-thyroid peroxidase (TPO) antibodies, both of which are highly specific for their individual diseases processes[13]. Betterle et al explored the prevalence of specific combinations of endocrinopathies occurring together in APS type 2[11]. Findings revealed that Addison's disease and an autoimmune thyroiditis leading to hypothyroidism were most likely to occur together with a prevalence of 56.1%, whereas the combination of Addison's disease, Grave's disease and type 1 diabetes were least likely to occur together with a prevalence of 2%[11]. Unlike our patient, 50% of individuals diagnosed with autoimmune primary AI may not immediately fulfill criteria for APS type 2[13]. Because of this, individuals with primary AI should be screened every five years for the development of hypothyroid disease and diabetes mellitus[13]. Primary ovarian insufficiency may also be seen with APS, most commonly in APS type 3 found in 10-40% of cases[14]. The diagnosis can be made in those with irregular menses and a post-menopausal FSH level[14]. Although our patient did not meet diagnostic criteria, an FSH level should be obtained in patients with APS.

Upon further review our patient's case and medical history as noted above, an emergent right salpingo-oophorectomy was performed during a pregnancy 10 years prior for an ovarian mass ultimately revealing squamous cell carcinoma (SCC) in the setting of an immature ovarian teratoma. After further discussion with the patient, we realized that contents of the mass may have seeded in the peritoneum during removal. The patient was not known to be hypothyroid or have symptoms consistent with likely Addison's disease at that time. This raised the question as to whether teratoma formation may lead to the development of autoimmune conditions. Upon further literature review, Morrissey at al described the development of an ovarian teratoma leading to the development of hyperthyroidism co-occurring with Hashimoto's thyroiditis[15]. Dulcey et al describes the development of autoimmune encephalitis secondary to autoantibodies against the N-methyl-D-aspartate receptor[16]. Researchers hypothesized that tumor necrosis may have led to neuronal antigen formation[16]. Our case, along with the cases described above, present an interesting topic regarding the predisposition to the development of autoimmune conditions in the setting of ovarian teratomas. Future research is needed to explore this connection.

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