We report a 67-year-old woman who presented with adrenal crisis as a manifestation of autoimmune polyglandular syndrome 2, a polygenic disorder characterized by concurrent primary adrenal insufficiency and either autoimmune thyroid disease or type 1 diabetes mellitus.

**CASE REPORT**

A 67-year-old woman with primary adrenal insufficiency (AI), hypothyroidism, non–insulin-dependent diabetes mellitus (DM), and dyslipidemia presented to our emergency department with symptomatic hypotension and presyncope associated with a 2-week history of postprandial nausea, vomiting, diarrhea, and abdominal cramping and a 20-pound unintentional weight loss. Her initial diagnosis of AI was made by a cosyntropin stimulation test during a hospital admission for hypotension and volume depletion 6 years earlier. She was discharged on hydrocortisone, and later fludrocortisone was added. Three months prior to the current presentation, hydrocortisone was discontinued in favor of fludrocortisone monotherapy for unclear reasons. Subsequently, she struggled with symptomatic hypotension, with her peak systolic blood pressure rarely exceeding 100 mm Hg; this persisted despite doubling of the fludrocortisone dose from 0.1 to 0.2 mg/day.

Upon initial evaluation, the patient’s blood pressure was 80/50 mm Hg and her heart rate was 60 beats/min. Initial laboratory studies were significant for a serum potassium level of 2.3 mmol/L (normal range, 3.5–5.1 mmol/L) and magnesium of 1.3 mg/dL (normal range, 1.8–2.4 mg/dL); her serum sodium, chloride, and bicarbonate levels were within normal limits. Serum cortisol drawn at 4:00 AM was 3.4 μg/dL (normal range, 3.7–19.4 μg/dL). Computed tomography of the abdomen revealed atrophied adrenal glands but no other explanation for her gastrointestinal symptoms (Figure 1).

The patient was given 3 L of normal saline and 100 mg of hydrocortisone intravenously, started on a norepinephrine infusion, and admitted to the intensive care unit. Subsequent management included continuation of hydrocortisone at a dose of 100 mg every 8 hours, resumption of thyroid hormone replacement, aggressive potassium repletion, and rapid weaning of norepinephrine. Her diarrhea resolved and no source of infection was identified. Hydrocortisone was tapered to an oral maintenance dose of 20 mg every morning and 10 mg every afternoon. Upon discharge, an endocrinology referral was made due to suspicion for autoimmune polyglandular syndrome-2 (APS-2).

**DISCUSSION**

Adrenal crisis (AC) is defined as an acute deterioration in a patient with AI associated with absolute or relative hypotension that improves following parenteral glucocorticoid administration (1). Other manifestations include fatigue, weakness, fever, altered sensorium, anorexia, nausea, vomiting, secretory diarrhea, abdominal pain, hyponatremia, hyperkalemia, metabolic acidosis, and rarely hypoglycemia (2). The combination of abdominal pain and fever may lead to an incorrect diagnosis of acute abdomen and potentially catastrophic surgical exploration (3).

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Hypotension results not only from hypovolemia but also from deficiency of cortisol itself, which exhibits a variety of genomic and nongenomic effects on vascular tone (4). Hypokalemia results from renal salt wasting, volume depletion, and resultant hypersecretion of antidiuretic hormone (ADH) caused by aldosterone insufficiency. Additionally, cortisol exerts direct and indirect negative feedback on ADH secretion; thus, its deficiency also leads to elevated ADH levels (5). Hyperkalemia is attributable to the loss of aldosterone, which normally promotes the urinary excretion of dietary potassium. In our patient, these classic abnormalities were not observed. Her normal serum sodium and low serum potassium levels may be explained by zealous mineralocorticoid replacement in combination with chronic gastrointestinal potassium and magnesium losses.

Common precipitants of AC include infection, surgical procedures, trauma, and abrupt withdrawal of glucocorticoid therapy (2). AC occurs more frequently in patients with primary compared to secondary AI, likely reflecting residual glucocorticoid secretion in the latter (1, 6). In a large German retrospective cohort study, the incidence of AC was higher in patients with APS-2 and highest in those with APS-2 and type 1 DM (6).

It is crucial that diagnostic testing not cause a delay in treatment. When AC is suspected, intravenous fluids (1 L normal saline in the first hour followed by continuous administration) and glucocorticoids (100 mg of hydrocortisone followed by 200 mg over 24 hours as a continuous infusion or in divided doses every 6 hours) should be administered promptly with concurrent testing of serum chemistries, cortisol, and adrenocorticotropic hormone (7). Long-term maintenance therapy usually consists of oral hydrocortisone (15 to 25 mg/day) or cortisone acetate (20 to 35 mg/day) in two or three divided doses. Most patients also require fludrocortisone at a dose of 0.05 to 0.2 mg/day (7). It cannot be overemphasized that patients with primary AI must never discontinue glucocorticoid replacement for any reason. As the present case illustrates, discontinuation of glucocorticoid therapy can have disastrous consequences despite adequate mineralocorticoid replacement.

The autoimmune polyglandular syndromes are a group of disorders characterized by endocrine and nonendocrine immune-mediated dysfunction. Three main syndromes have been described. Autoimmune polyglandular syndrome-1 (APS-1) is an autosomal recessive disorder caused by mutations in the autoimmune regulator (AIRE) gene, which results in a loss of central tolerance, the process by which self-reactive T cells are eliminated in the thymus during early differentiation. It usually manifests during infancy with mucocutaneous candidiasis; primary AI and hypoparathyroidism occur later. APS-1 is associated with other autoimmune diseases including type 1 DM, vitiligo, alopecia, hepatitis, pernicious anemia, and primary hypothyroidism. The diagnosis is made by genetic testing. Hormone replacement and aggressive treatment of mucocutaneous candidiasis are the mainstays of treatment (8). APS-2, also known as Schmidt syndrome, is the most common autoimmune polyglandular syndrome. In contrast to APS-1, APS-2 is a polygenic disorder associated with particular HLA class II haplotypes in addition to mutations in several non-HLA genes. Onset is during adulthood, and the individual endocrine and nonendocrine components may develop years or decades apart. Primary AI plus either autoimmune thyroid disease or type 1 DM are the principal manifestations; associated diseases include celiac disease, pernicious anemia, myasthenia gravis, vitiligo, and alopecia. Treatment focuses on the identification and management of the component autoimmune conditions (8). The third form, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by mutations in the forkhead box P3 (FOXP3) gene resulting in functional or quantitative deficiency of regulatory T cells. The disease manifests in the first days to months of life with severe autoimmune enteropathy, dermatitis, and type 1 DM and may be rapidly fatal if untreated. Immunosuppressive drugs can be effective in ameliorating autoimmune and allergic disease but are associated with significant toxicity. Restoration of regulatory T-cell function via hematopoietic stem cell transplantation offers the potential for cure (8).