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CASE REPORT

Acute Diarrhea Isn't Always Infectious: An Atypical Presentation of Adrenal Insufficiency

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Abstract

Adrenal insufficiency can be a primary or secondary disorder occurring from a hormone deficiency or suppression of the hypothalamic–pituitary axis from various etiologies. The diagnosis can be challenging given the lack of specificity and indolence of symptoms. Diarrhea is not a typical presenting symptom of adrenal insufficiency and can be overlooked as an infectious disease during an adrenal crisis. Herein we present a patient with an undiagnosed adrenal insufficiency who presented with subacute diarrhea during an adrenal crisis after a dental procedure and esophagogastroduodenoscopy.

Keywords: Adrenal insufficiency, Addison disease, Endocrinopathies, Autoimmune disease, Acute diarrhea, Adrenal crisis

Learning points

- Adrenal insufficiency presents with non-specific symptoms and is often diagnosed at the time of an adrenal crisis.
- Adrenal Crisis confers a high mortality rate and a high index of suspicion is imperative, even with atypical presentations, such as diarrhea.
- Diarrhea is a less common manifestation of adrenal insufficiency, but adrenal insufficiency should remain on the differential when a patient fits the clinical picture.
- Use caution proceeding with an extensive infectious workup if there is other clinical or laboratory stigmata of adrenal insufficiency or other autoimmune diseases.

1. Introduction

Adrenal insufficiency (AI) was first discovered in 1855, when Thomas Addison reported clinical findings such as vitiligo and adrenal shrinkage of autopsy patients, which he later referred to as "Addison's Disease.[1]" Following this, the mortality was high for patients with Addison's Disease until clinical trials proved a therapeutic benefit with the use of steroids in the 1940's and 1950's.[1] Today, although much more is known about AI, the mortality is still high and the disease is underdiagnosed due to diagnostic clinical challenges.[2,3]

AI can occur at any age, but often is diagnosed between 20 years and 50 years of age.[2,3] It is more commonly diagnosed in middle aged women.[2,3] During acute stress, corticotropin-releasing hormone (CRH) is released from the hypothalamus to stimulate the anterior pituitary to secrete adrenocorticotropic hormone (ACTH).[4] This in turn signals cortisol to be secreted from the zona fasciculata of the adrenal cortex.[4] Primary adrenal insufficiency (PAI) or Addison's disease is characterized by low cortisol and high ACTH from the destruction of the adrenal glands.[4] The prevalence of PAI is approximately 82–144 per million, and the most common cause after puberty is autoimmune disease in developed countries.[2] Prior to puberty, congenital adrenal hyperplasia is the most common cause.[3]

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Autoimmune disease can be isolated adrenalitis in approximately 30–40% of cases, or can be in combination with other endocrinopathies, such as thyroid disease, Type 1 Diabetes Mellitus, premature ovarian insufficiency, celiac disease, pernicious anemia or alopecia.[2,3] The pattern of heritability is similar to these other autoimmune diseases, particularly celiac disease given the genes that are expressed in immune and inflammatory cells, particularly T-cells and MHC Class II genotypes.[3] A Norwegian study by Erichsen et al. demonstrated an incidence of 58.7% in females with PAI who also had autoimmune hypothyroidism.[2] Infections also play a role in the development of autoimmune PAI, in which gastrointestinal infections, *Mycobacterium tuberculosis*, HIV, or CMV can even result in chronic adrenalitis and fibrosis, or bilatearl adrenal hemorrhage, as seen in *Meningococcal* meningitis.[4] PAI can also be caused by infiltrative diseases, such as sarcoidosis, amyloidosis, or could iatrogenic from ketoconazole, rifampin, phenytoin, diuretics, checkpoint inhibitor immunomodulators, or mitotane.[4] Less common etiologies include pregnancy, trauma, sepsis, surgery, physical overexertion and dehydration or other endocrinopathies, such as Diabetic Ketoacidosis or myxedema coma.[4]

PAI may go undiagnosed for many years, as the symptoms are nonspecific and are indolent in nature.[1] Often a definitive diagnosis is not clear until a patient presents with adrenal crisis, which is a life-threatening complication.[1,3] Roughly half of the patients who present to the emergency department with an acute crisis and shock are undiagnosed with Addison disease and/or other autoimmune diseases and endocrinopathies, such as diabetes, or hypothyroidism.[4] Laboratory studies will reveal electrolyte derangements such as hyponatremia, hyperkalemia, hypoglycemia, acute renal injury, non-anion gap metabolic acidosis, eosinophilia, and often these can be explained by other more common etiologies, further delaying the diagnosis of PAI.[4] A serum ACTH and cortisol measurement during an acute crisis is sufficient to diagnose preliminary adrenal insufficiency, although a formal diagnosis should be made after a crisis has resolved.[4] Treatment should never be delayed to make a diagnosis with serological testing.[4]

Herein we present a case of primary adrenal insufficiency diagnosed after an extensive workup for subacute diarrhea.

2. Case presentation

A 72-year-old female with past medical history of tobacco use, stage II chronic kidney disease, hypothyroidism and depression presented to the Emergency Department (ED) with a two-week history of worsening dizziness, non-bloody, non-bilious emesis and diarrhea after being discharged from a hospitalization two weeks prior to presentation. The patient was in her usual state of health until two months prior, when she went for a dental procedure and was treated with a course of amoxicillin. She subsequently developed episodes of loose, non-bloody, non-mucoid bowel movements with no associated abdominal pain, anorexia, nausea or vomiting. At that time, she was prescribed omeprazole by her primary care physician in Puerto Rico. The diarrhea then progressed to watery bowel movements three times daily, now accompanied by nausea and vomiting occurring after every meal. She also had cramping abdominal pain, localized to the periumbilical region without radiation. She was hospitalized at another hospital in the United States, and was diagnosed with duodenitis after undergoing an esophagogastroduodenoscopy (EGD). She completed a seven-day course of metronidazole and cefuroxime upon discharge, however the symptoms persisted. She denied any blood in the stool and had a colonoscopy four-years prior that was reportedly normal. Review of systems was also significant for an unintentional- 20-pound weight loss over the last month. On arrival, she was hemodynamically stable, afebrile and examination showed a well appearing Hispanic woman with diffuse abdominal tenderness to deep palpation of the periumbilical region. Bowel sounds were normoactive, there was no organomegaly and peritonitis was absent. The patient also had thickened and shiny skin overlying her cheek bones. Laboratory studies were significant for hyperkalemia, non-anion gap metabolic acidosis, and acute kidney injury (Table 1). She was initially admitted for acute kidney injury due to hypovolemia in the setting of gastrointestinal loss and orthostatic hypotension was found. A computerized tomography (CT) of the abdomen and pelvis without contrast demonstrated mesenteric panniculitis without other acute findings to explain her diarrhea or presentation otherwise.

An extensive infectious diarrhea workup, including stool cultures, ova and parasites, stool electrolytes and pH, *Clostridioides difficile, Giardia, Cryptosporidium,* and *Vibrio* were all unremarkable. She underwent an EGD, which showed a small hiatal hernia, mild inactive gastritis and negative for *Helicobacter pylori*, non-bleeding angioectasia of the stomach and gastric mucosal atrophy. The colonoscopy showed small tubular adenomas of the descending and sigmoid colon and internal hemorrhoids, but were otherwise unremarkable. At this

Table 1. Admission labs.

Comprehensive Metabolic Panel	Value (Reference Range)	Complete Blood Count	Value (Reference Range)
Sodium	131 mEq/L (135–145)	White Blood Cells	7.6 × 103/mm3 (4.5–11)
Potassium	6.2 mEq/L (3.5–5.0)	Red Blood Cells	4.82 × 106/mm3 (4–5.33)
Chloride	118 mEq/L (98–107)	Hemoglobin	14.0 g/dL (12–16)
Bicarbonate	24 mEq/L (21–31)	Hematocrit	42.3% (36–46)
Glucose	104 mg/dL (70–110)	MCV	87.8 fL (80–100)
Calcium	10.7 mg/dL (8.6–10.3)	MCH	29.0 pg (26–32)
Blood Urea Nitrogen	49 mg/dL (7–23)	MCHC	33.1 g/dL (31–37)
Creatinine	3.26 mg/dL (0.60–1.30)	RDW	12.4% (0.5–16.5)
Total Bilirubin	0.7 mg/dL (0.3–1.1)	Platelets	303 K/mm3 (140–440)
Total Protein	7.8 g/dL (6.4–8.4)	MPV	10.8 fL (7.4–10.4)
Albumin	4.4 g/dL (3.5–5.7)	Neutrophil Auto	52.6% (36–75)
Alkaline phosphatase	43 unit/L (34–104)	Lymph Auto	33.3% (24–44)
Aspartate aminotransferase	32 unit/L (13–39)	Monophil Auto	9.4% (4–10)
Alanine aminotransferase	10 unit/L (7–52)	Eosinophil Auto	3.7% (0–5)
Phosphorous	5.4 mg/dL (2.5–5.0)	Basophil Auto	0.9% (0–2)
Magnesium	1.9 mg/dL (1.7–2.5)	Immature Granulocytes	0.1% (0–0.6)
Serum Osmolality	293 mOsm/kg (283–299)	Segmented Neutrophils	None
		Bands Manual	None

stage, the working diagnosis was chronic diarrhea of unknown etiology. The patient then developed acute encephalopathy with visual hallucinations over the course of three days following her EGD. CT of the head was unremarkable, however the patient scored 21 on a Mini-Mental Examination, and thus it was presumed she may have hospital acquired delirium with underlying early dementia. The diarrhea persisted however, and given the concomitant persistent hypotension, hyperkalemia and altered mental status, a morning cortisol level and serum ACTH level was obtained, revealing primary adrenal insufficiency (Table 2). Although these levels were confirmatory, co-syntropin was administered and serum cortisol was ordered for the 30-min and 60-min mark, however were obtained incorrectly with the morning labs by mistake. Interestingly, anti-adrenal antibodies were negative. A repeat CT of the abdomen did not demonstrate any pathology of the adrenal glands and they were of normal size. Endocrine was consulted and she was treated with fludrocortisone 0.1 mg daily and hydrocortisone 15 mg in the morning and 5 mg at night. With the commencement of steroid therapy, the patient had normalization of her stool consistency, resolution in vomiting, improvement in mentation, laboratory values and vital signs. She was optimized for discharge to a subacute rehabilitation facility with scheduled follow up appointments with Endocrine and Nephrology services in the outpatient setting and was instructed on wearing an alert bracelet for her newly diagnosed primary adrenal insufficiency.

Table 2. Autoimmune labs.

Morning Cortisol	0.4 mcg/dL (6–23)
ACTH	1685.0 pg/mL (7.2–63.3)
Cortisol 30 min- in error	0.4 mcg/dL (3–16)
Cortisol 60 min- in error	0.5 mcg/dL (3–24)
TSH	10.057mcIntlUnit/mL (0.450–5.330)
Free T4	0.69 ng/dL (0.61–1.12)
HIV	Negative
QuantiFERON Gold Tuberculosis	Negative
Aldosterone	<1.0 ng/dL (0–30)
Renin	<0.167 ng/mL/hr (0.167–5.380)
Anti-adrenal Antibody	Negative
Urine Alpha 1/2 globulin	Negative
Urine Beta 1/2 globulin	Negative
Serum Alpha 1/2 globulin	Negative
Serum Beta 1/2 globulin	Negative
Kappa Light Chains	41.4 mg/L (3.3–19.4)
Lambda Light Chains	31.4 mg/L (5.7–26.3)
Urine Gamma globulin	Negative
M spike protein	Negative

3. Discussion

50–75% of patients are undiagnosed with AI at time of hospitalization for an adrenal crisis.[2,4] Diagnosis is typically delayed or misdiagnosed due to ambiguity and slow progression of symptoms.[2] A Norwegian registry of autoimmune PAI determined that 19% of patients had symptoms between one to five years prior to diagnosis, and 59% were diagnosed within a six-month period after symptom onset.[2] Our patient did not present in an adrenal crisis, however developed worsening symptoms after her dental procedure two months prior to presentation, endoscopy two weeks prior to presentation, and then suffered an adrenal crisis while inpatient after the second endoscopy. Her symptoms were initially characterized by weight loss, fatigue, anorexia, but her predominant symptoms

were diarrhea and abdominal pain. which is what prompted the initial endoscopy at the previous hospital. The diagnosis was masked by her recent travel from Puerto Rico, hospitalizations and recent antibiotic use, all of which could have contributed to her subacute diarrhea, anorexia and weight loss. These risk factors were initially concerning for *C. difficile,* or another infectious diarrheal pathogen however extensive workup was negative.

Diarrhea as the predominant symptom is uncommon in AI.[5] Diarrhea, however, is commonly seen as the initial symptom in other endocrinopathies.[5] The type of diarrhea varies depending on etiology.[5] Pancreatic endocrine tumors, such as somatostatinomas, VIPomas or glucagonomas produce watery or secretory diarrhea, compared to diabetics who may experience constipation or high-voluminous diarrhea in insulin-dependent diabetes, due to the disruption of colonic motility and intestinal neuropathy.[5] Patients with hyperthyroidism may complain of malabsorption and steatorrhea compared to the hypothyroid patient who often has flatulence and constipation alternating with obstructive diarrhea and fecal incontinence.[5] In AI, the watery diarrhea and malabsorption lead to electrolyte derangements.[5] One study demonstrated diarrhea as a complication of PAI in only 16% of patients, and it has been shown to precipitate an adrenal crisis due to volume contraction.[6] Only one other case report published diarrhea as a primary manifestation of adrenal insufficiency, except it described in two patients using exogenous steroids after surgical transplantation.[6]

Once AI is suspected, a cortisol level and ACTH level should be obtained.[1] A diagnosis can be made if the basal cortisol is less than 3–5 mg/dL and a plasma ACTH is greater than 100 pg/mL.[1] This was the case in our patient with a morning cortisol level of 0.4 mcg/dL and an ACTH level of 1685 pg/mL. A short-ACTH stimulation test should be ordered in all patient where PAI is considered, but may not be always necessary if the basal cortisol and ACTH are initially confirmatory.[1] Otherwise, the ACTH is helpful to distinguish between primary and secondary AI, but urinary cortisol should not be obtained due to its low sensitivity.[1] In our patient, unfortunately the serum cortisol intended to be drawn at the 30-min and 60-min mark was obtained prior to administration of the co-syntropin, and thus the short-ACTH stimulation test was negligible. To detect autoimmune disease, the adrenal cortex autoantibodies are the gold standard, however are positive in only 40–80% of patients with idiopathic PAI, and thus the test is not sensitive.[1] Conversely, the 21-OH autoantibodies are highly sensitive and specific for autoimmune AI, but cannot be used as a marker of disease severity or responsiveness to treatment.[1] Our patient tested negative for the adrenal cortex auto-antibodies, but was unfortunately never tested for 21-OH. Although her adrenal glands were of normal size and character on imaging, autoimmune AI cannot be definitively excluded at this time. It is still presumed that our patient had primary AI.

It is also important to note that her constellation of constitutional symptoms, including the objective findings of skin thickening over the face are also concerning for another concomitant autoimmune disease.[4] Her hypothyroidism may have confounded the diagnosis of primary AI, however other diagnoses such as scleroderma or systemic lupus erythematous should have been considered. Many patients with one autoimmune disease have a concomitant autoimmune disease affecting other organ systems.[4] Although Celiac disease has overlapping genetic predispositions to PAI, and was appropriately excluded in our patient, these other tests were not performed, and this limits our study.

Approximately 5–10 per 100 patients with chronic adrenal insufficiency develop an adrenal crisis per year.[4] The mortality rate is approximately 0.5 per 100 patients per year, which is secondary to physiological derangements from an acute depletion of cortisol.[4] Previous studies have suggested that those with primary adrenal insufficiencies are at a higher risk of developing an Addisonian Crisis compared to those with secondary etiologies.[4] It is characterized as an acute change in physiological status, quickly progressing from nonspecific symptoms of fatigue, weakness, nausea, vomiting, abdominal pain, back pain, diarrhea, dizziness, hypotension, syncope and metabolic encephalopathy with sometimes obtundation and shock.[4] Initially, it was thought that our patient had hospital-acquired delirium or early signs of dementia because her family also described a cognitive decline during the two months prior to presentation. The most frequent causes of adrenal crisis are surgical and dental procedures or infections such as gastroenteritis and food poisoning.[3] Our patient's adrenal crisis was likely multifactorial: she underwent a dental procedure, two EGD's, a tooth infection and duodenitis both treated with antibiotics, and possibly an intestinal infection at some point given the panniculitis seen on imaging. It is likely that her symptoms of adrenal insufficiency started many months prior to her decline, however fortunate that she was already monitored in the hospital at the time of her adrenal crisis.

4. Conclusion

Often adrenal insufficiency is underdiagnosed, or diagnosed at the time of an adrenal crisis. An adrenal crisis is a life-threatening complication of adrenal insufficiency and carries a high mortality rate. It is imperative for clinicians to consider adrenal insufficiency as a differential in patients with non-specific symptoms such as diarrhea. Moreover, adequate patient education on managing adrenal insufficiency during times of acute stress is of utmost importance.

Consent

As this is a case report, consent was obtained for the purpose of this paper.

Author contribution

Dr. Tagliaferri is the article guarantor. All authors performed the literature review and wrote the manuscript. All authors assisted in the collection of the patient's clinical data. All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at St. Joseph's University Medical Center at the following address:

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Conflict of interest

The authors report no conflict of interest. Ethical review is not necessary, because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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References

1. Saverino S, Falorni A. Autoimmune Addison's disease. *Best Pract Res Clin Endocrinol Metabol*. 2020;34, 101379. https://doi.org/10.1016/j.beem.2020.101379.
2. Martin-Grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: physiology, clinical presentation and diagnostic challenges. *Clin Chim Acta*. 2020;505:78–91. https://doi.org/10.1016/j.cca.2020.01.029.
3. Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. *Lancet*. 2021;397:613–629. https://doi.org/10.1016/s0140-6736(21)00136-7.
4. Rathbun KM, Nguyen M, Singhal M. *Addisonian crisis. StatPearls. StatPearls Publishing Copyright © 2022*. Treasure Island (FL): StatPearls Publishing LLC.; 2022.
5. Sharma S, Longo WE, Baniadam B, Vernava 3rd AM. Colorectal manifestations of endocrine disease. *Dis Colon Rectum*. 1995;38:318–323. https://doi.org/10.1007/bf02055611.
6. Sikanderkhel S, Choudhry MW, Valentine V, Al-Dossari G, Khalife WI. Diarrhea-An uncommon presentation of tertiary adrenal insufficiency following heart transplantation. *J Card Surg*. 2017;32:522–525. https://doi.org/10.1111/jocs.13175.