VOLUME 03 ISSUE 01 (2024)

AMERICAN JOURNAL OF MEDICAL SCIENCE AND INNOVATION (AJMSI)

ISSN: 2836-8509 (ONLINE)

PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

American Journal of Medical Science and Innovation (AJMSI)

Volume 3 Issue 1, Year 2024
ISSN: 2836-8509 (Online)
DOI: https://doi.org/10.54536/ajmsi.v3i1.2773
https://journals.e-palli.com/home/index.php/ajmsi

Miliary Tuberculosis Causing Presumed Primary Adrenal Insufficiency and Addisonian Crisis: A Case Report from Rural Kenya

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Article Information

Received: April 05, 2024
Accepted: May 10, 2024
Published: May 14, 2024

Keywords

Primary Adrenal Insufficiency, Addison's Disease, Adrenal Crisis, Addisonian Crisis, Miliary Tuberculosis, Tuberculous Adrenal Insufficiency, Glucocorticoid, Kenya

ABSTRACT

Primary adrenal insufficiency (Addison's disease) is characterized by inadequate production of cortisol from the adrenal glands due to diseases of the adrenal gland. Due to the insidious onset and non-specific nature of the symptoms of adrenal insufficiency, diagnosis is often delayed until patients present with an adrenal crisis. The three most common causes are autoimmune adrenalitis, infections, e.g., disseminated tuberculosis, HIV, systemic mycoses, and adrenal hemorrhage or infarction. Miliary tuberculosis of the adrenal gland occurs in high-TB burden populations by hematogenous spread of tuberculous bacilli to the gland, causing caseous necrosis, or by extra-adrenal infection and rifampicin-induced adrenal insufficiency. In this study, we report on the case of a middle-aged woman in rural Kenya who initially presented with missed features of adrenal insufficiency and subsequently went into an adrenal (Addisonian) crisis, which was successfully managed with glucocorticoids, fluids, and supportive therapy.

INTRODUCTION

Adrenal insufficiency is characterized by an absolute or relative deficiency in the production of glucocorticoid (cortisol) from the adrenal cortex due to destruction of the adrenal cortex or a lack of stimulation of adrenocorticotrophic hormone (ACTH) (Hahner *et al.*, 2021). This can be primary (caused by diseases of the adrenal gland), secondary (caused by impaired secretion of ACTH by the pituitary gland, e.g., in panhypopituitarism from any cause, brain injury, high dose progestins, etc.), or tertiary (caused by interference with the secretion of corticotropin-releasing hormone (CRH) by the hypothalamus, typically by exogenous administration of high dose glucocorticoid therapy) (Grossman, 2010; Hahner *et al.*, 2021; Joseph *et al.*, 2016). Primary adrenal insufficiency (Addison's disease) is caused by the destruction or dysfunction of the adrenal cortex and manifests with features of cortisol and aldosterone deficiency. The most common causes of Addison's disease are autoimmune adrenalitis, infections (e.g., disseminated tuberculosis, HIV, and disseminated fungal infections like histoplasmosis), adrenal hemorrhage and infarction, metastatic cancers (e.g., primary colon, breast, lung, gastric, and lymphoma), and drugs, e.g., ketoconazole, fluconazole, rifampicin, etc. (Barthel *et al.*, 2019). Tuberculosis causing Addison's disease is due primarily to the hematogenous spread of tubercle bacilli into the adrenal cortex, leading to caseous necrosis of the glands, or by extra-adrenal infection, and as a by-product of anti-tuberculous therapy with rifampicin (Vinnard & Blumberg, 2017). Typically, >90% of the gland has to be destroyed before symptoms of adrenal insufficiency ensue. Although the incidence of tuberculous Addison's disease has been declining globally due to more effective TB management (Nomura *et al.*, 1994), TB is still a major cause of adrenal insufficiency in high TB burden populations, e.g., Kenya (Enos *et al.*, 2018). In a 2024 systematic review, the pooled prevalence of adrenal insufficiency in tuberculosis was 33% (Kibirige *et al.*, 2024). Clinical features of adrenal insufficiency are often insidious and nonspecific and may include features of adrenal crisis or chronic adrenal insufficiency. Adrenal crisis is predominantly characterized by shock as well as multisystemic features (Burke, 1985). (See Table 1). Patients with chronic primary adrenal insufficiency have an insidious onset and gradual development of features of both cortisol and aldosterone deficiency. A diagnosis of adrenal insufficiency is often delayed due to the non-specificity of the clinical features, e.g., gastrointestinal symptoms (like nausea, vomiting, anorexia, vomiting, abdominal pain, etc.), fatigue, weight loss, musculoskeletal pains, and neuropsychiatric symptoms like altered mental status, psychosis, hallucinations, etc. Nonetheless, the occurrence of hyperpigmentation, salt craving, and postural hypotension strongly suggests primary adrenal insufficiency. The diagnosis of adrenal insufficiency is primarily by the adrenocorticotropic hormone stimulation test (Synacthen or Cosyntropin tests) (Ospina *et al.*, 2016). The management of adrenal insufficiency primarily involves the use of corticosteroids (hydrocortisone), mineralocorticoids, supportive therapy, and the treatment of underlying diseases, e.g., the use of anti-TB drugs as

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per local guidelines (Lewis *et al.*, 2023). Comprehensive guidance for the diagnosis and management of adrenal insufficiency can be found in 'The Clinical Guidelines Subcommittee of the Endocrine Society' (Bornstein *et al.*, 2016).

Table 1: Clinical and Laboratory Findings Suggesting Adrenal Crisis

Dehydration, hypotension, or shock out of proportion to the severity of the current illness
Nausea and vomiting with a history of weight loss and anorexia
Abdominal pain, so-called "acute abdomen"
Unexplained hypoglycemia
Unexplained fever
Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
Hyperpigmentation, or vitiligo
Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure

Adapted from: Burke CW. Adrenocortical insufficiency. Clin Endocrinol Metab 1985; 14:947. (Burke, 1985)

Case Presentation

Presenting Illness and Physical Examination

A 52-year-old woman, mother of four, and businesswoman from Kabatini, Nakuru County, Kenya, presented to us in September 2023 with altered mental status. She had a preceding 2-week history of recurrent post-prandial and unprovoked non-bilious vomiting, watery, non-bloody diarrhea (2-3 episodes every 2-3 days), generalized abdominal pains, progressive lethargy, and a day-long history of visual hallucinations. These occurred on a background history of recurrent dry cough, drenching night sweats, a 4kg weight loss, and anorexia in the 6 weeks prior. There was no clear history of food poisoning. She neither smoked nor took ethanol. On initial examination, she was severely dehydrated with a tachycardia of 113 bpm, a blood pressure of 117/77 mmHg, afebrile, normal oxygen saturation in room air, and a random blood sugar of 74 mg/dL. Her abdomen was diffusely tender but soft, with no organomegaly and no features of peritonism. Her Glasgow coma scale was 12/15; she had no meningism and no focal neurology, though she was actively hallucinating during the exam. Her skin had no rashes or peripheral hyperpigmentation. She was cool to touch in the peripheries with low-volume pulses, but she had normal heart sounds. She had orthostatic hypotension, with her BP dropping from 117/77 mmHg to 90/58 mmHg from recumbent to upright positions. The rest of the exam was unremarkable.

Diagnostic Workup and Management

Her baseline laboratory tests showed a normal complete blood count (CBC), an elevated ESR of 50 mm/hr., no malaria parasites on a blood smear microscopy, a negative HIV rapid test, and stool studies showed no ova or parasites and no blood or mucus. She also had normal liver function tests. Her creatinine was elevated at 1.9 mg/dL, but she had profound hyponatremia with serum Na^+ of 109 mmol/L (135-145), K^+ of 4.1 mmol/L (3.5-5.5), and Cl^- of 75 mmol/L (95-108). Her lumbar puncture with cerebrospinal fluid analysis was normal. Her chest x-ray showed a miliary pattern bilaterally consistent with miliary tuberculosis (see Figure 1). An abdomino-pelvic ultrasound and a gastroscopy were both unremarkable. A diagnosis of miliary tuberculosis with acute gastroenteritis complicated with pre-renal acute kidney injury and severe symptomatic hyponatremia was made. Following a successful resuscitation, she was started on anti-TB therapy as per local guidelines, with Rifampicin, Isoniazid, Ethambutol, Pyrazinamide, and pyridoxine (the latter to mitigate isoniazid-induced peripheral neuropathy), and supportive care. The hyponatremia was successfully managed with a hypertonic saline infusion. She was discharged five days later while lucid and in normal clinical status.

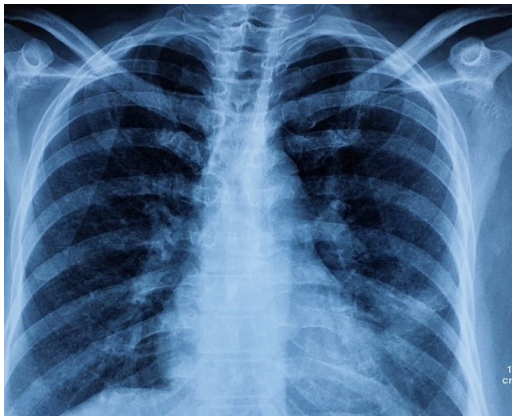

Figure 1: Initial CXR showing bilateral diffuse miliary infiltrates, consistent with miliary tuberculosis

Re-admission in an Addisonian Crisis

However, she was re-admitted 1 month later in a comatose state (GCS of 8/15) with hypothermia (a temperature of 34°C), a tachycardia of 104 bpm, and hypotension (BP of 85/63 mmHg, which dropped to a nadir of 60/42 mmHg). She had a reported 3-week history of recurrent post-prandial vomiting but no diarrhea, vague abdominal pains, dysuria, anorexia but craving salt and licking it several times, lethargy, and confusion. Her urinalysis showed leukocytosis and positive nitrites consistent with cystitis. She had neutrophilic leukocytosis with a total leucocyte count of $13x10^3u/L$, severe hyponatremia with Na^+ of 100 mmol/L, K^+ of 5.7 mmol/L, Cl^- of 79 mmol/L, and a normal creatinine of 0.6 mg/dL. A thyroid profile and an uncontrasted CT scan of the brain were normal. She initially had a persistently low random glucose of 70 to 90 mg/dL, hypotension needing inotropic support, and hyponatremia with borderline hyperkalemia. In light of these, we made a presumptive clinical diagnosis of adrenal crisis precipitated by cystitis on the background

of adrenal insufficiency caused by miliary tuberculosis. Due to a lack of finances, we could not do further confirmatory tests. The patient was put on intravenous hydrocortisone, normal saline, and supportive therapy. Six days later, she had a full resolution of the adrenal crisis and was discharged home stable. See Table 2 for a summary of her blood pressure readings, significant laboratory results, and the specific interventions given.

During outpatient follow-up, we kept her on tapered doses of oral prednisone (the cheapest available option), with omeprazole and vitamin D/calcium combo tablets for gastroprotection and osteoprotection, respectively. We continued the TB treatment for 6 months as per local protocols and monitored her for any complications related to the steroid therapy. By the end of the 4th month of TB treatment, we stopped the steroids, and her subsequent serum electrolytes, blood pressure, and random blood glucose remained normal until the end of TB treatment and on follow-up so far. Her CXR has since normalized. (See Figure 2).

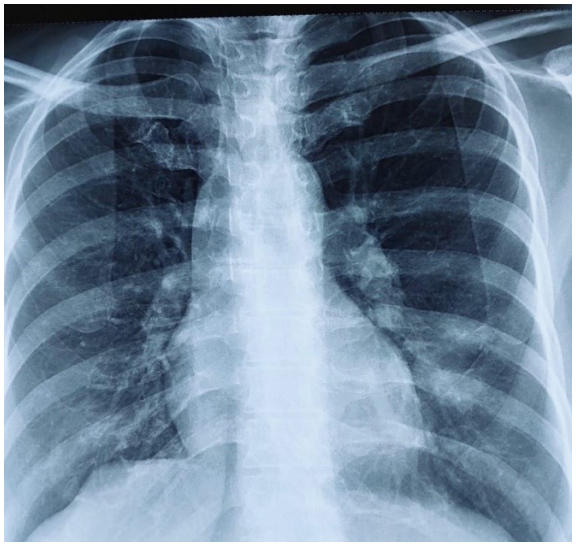

Figure 2: Repeat CXR done 4 months after initiating TB treatment showing a complete resolution of the miliary infiltrates

Table 2: Summary of Significant Blood Pressure, Laboratory Results, and Specific Interventions

Date	Blood Pressure (mmHg)	Creatinine (mg/dL) (0.5-1.0)	Sodium (mmol/L) (135-145)	Potassium (mmol/L) (3.5-5.5)	Glucose (mg/dL) (72-200)	Specific Interventions
30/9/2023	117/77, 90/58	1.9	109	4.1	7	3% NaCl, RHZE, B6, IVFs
3/10/2023	112/76		126	3.4		RHZE, B6, ORS
18/10/2023	116/76		133	4.8		RHZE, B6
6/11/2023	85/63, 60/42	0.6	100	5.7	131, 80	RHZE, B6, 3% NaCl Inotropes, IVFs, Abx
7/11/2023	92-138/55-72		114	5.9	70, 224, 86	RHZE, B6, 3% NaCl Inotropes, IVFs, Abx, Steroids
9/11/2023	124-148/64-84	0.7	126	5.8	145, 96, 78	RHZE, B6, 3% NaCl Inotropes, IVFs, Abx, Steroids
10/11/2023	96-122/62-70		136	4.4	264, 186, 144	RHZE, B6, IVFs, Abx, Steroids
23/11/2023	121/85		126	4.5	155	RHZE, B6, Steroids, ORS, Slow Na tabs
6/12/2023	126/85	0.7	126	4.0	146	RH, B6, Steroids, ORS, Slow Na tabs
5/1/2024	118/84	0.9	133	4.1	115	RH, B6, Steroids, Slow Na tabs
4/3/2024	119/64	0.9	147	4.8	130	RH, B6
3/4/2024	124/83	1.0	150	5.2	150	
8/4/2024	126/78		142	4.9	174	

KEY: 3% NaCl= 3% sodium chloride (hypertonic saline infusion), RHZE= rifampicin, isoniazid, pyrazinamide, ethambutol, B6=vitamin B6 (pyridoxine), IVFs=intravenous fluids (including dextrose and saline infusions), Abx=antibiotics, Inotropes=adrenaline infusion, Steroids=intravenous hydrocortisone or oral prednisone, ORS=oral rehydration salt, Slow Na tabs=slow sodium tablets.

DISCUSSION

The symptoms and signs of adrenal insufficiency are often non-specific and insidious in onset, and may go undetected until some physiological stress precipitates an adrenal crisis. Disseminated TB (e.g., miliary TB) remains an important cause of adrenal insufficiency in

high-TB burden populations (Anaforoğlu *et al.*, 2012; Enos *et al.*, 2018; Vinnard & Blumberg, 2017; Yokoyama *et al.*, 2009). In retrospect, during her first admission, our patient already had some clinical features of adrenal insufficiency. Her recurrent diarrhea and vomiting, abdominal pains, persistent hyponatremia despite replacement, and postural hypotension were all in keeping with adrenal insufficiency (Hahner *et al.*, 2021), even though acute gastroenteritis complicated with severe fluid and electrolyte anomalies could also explain them. She later presented with a classical adrenal (or Addisonian) crisis (Rathbun & Singhal, 2024) in her second admission, most likely precipitated by acute cystitis. The diagnosis this time was easily made on the basis of gastrointestinal symptoms, salt craving, persistent shock, hyponatremia, hyperkalemia, and hypoglycemia. (See Table 1). Adrenal crisis, principally presenting as shock, is a life-threatening emergency that requires urgent treatment with intravenous glucocorticoids, fluids, and supportive care (Rathbun & Singhal, 2024). Treatment must not be delayed for all suspected patients in order to perform any diagnostic tests, as it carries a high mortality rate of up to 10% (Ngaosuwan *et al.*, 2021). Biochemical tests for the diagnosis of adrenal insufficiency include measurement of cortisol levels, ACTH-stimulation assays, etc., as well as diagnostic tests to determine the underlying causes as per endocrinological society guidelines (Bornstein *et al.*, 2016). The glucocorticoid of choice is hydrocortisone (it has both glucocorticoid and mineralocorticoid properties), given as a bolus dose of 100mg, followed by 50mg every 6 hours for 24 hours (or 200 mg/24 hours as a continuous infusion), and thereafter tapered to clinical response. One may alternatively use intravenous methylprednisolone or dexamethasone (Bornstein *et al.*, 2016). In her case, we gave a bolus dose of intravenous hydrocortisone 200mg, followed by a maintenance dose of 100mg every 8 hours a day for 3 days, before de-escalating to oral prednisone (which is cheaper and more readily available). Whereas hyponatremia and hypokalemia are expected to resolve with hydrocortisone and normal saline infusions, in our patient, we administered a 3-day course of hypertonic saline to correct the profound hyponatremia causing altered mental status. This is in line with conventional practice (Adrogué *et al.*, 2022). We elected to keep her on oral slow sodium tablets until the complete resolution of the hyponatremia. The hypoglycemia resolved with the steroid and dextrose infusions. Hypotension caused by an adrenal crisis responds rapidly (usually within a few hours) to intravenous glucocorticoid and fluid administration. Our patient had persistent hypotension, most likely superimposed by urosepsis, and needed inotropic support with an adrenaline infusion and intravenous ciprofloxacin before a full resolution. Various society guidelines have protocols for tapering off the glucocorticoids following the resolution of an adrenal crisis, depending on whether the patient has known or unknown underlying adrenal insufficiency (Bornstein *et al.*, 2016). The principal determination is the clinical status of the patient and adequate monitoring. In our patient, we made a clinical decision to taper her prednisone from 20, 10, and 5 mg over a 4-month's duration as we took mitigating measures against the complications of the steroids. Rifampicin, which is the main drug in TB treatment, has been reported to induce adrenal insufficiency and adrenal crises (Campbell *et al.*, 2023; Kyriazopoulou *et al.*, 1984). Most of these cases occurred in patients with underlying adrenal insufficiency, and following adequate glucocorticoid replacement, the drug was continued safely with close patient monitoring. Our patient has successfully finished her TB therapy containing rifampicin for the past six months without recurrent adrenal insufficiency or crisis. We believe that with the cure of the TB, the adrenal glands have fully recovered their functions.

CONCLUSION

Primary adrenal insufficiency (Addison's disease) should be considered in patients on treatment for disseminated tuberculosis, who present with recurrent gastrointestinal symptoms, hyponatremia, hyperkalemia, salt craving, and postural hypotension. Adrenal crisis occurs when persistent hypotension and shock ensue in the setting of adrenal insufficiency and recent physiological stress. This carries a high mortality rate of up to 10%. When an adrenal crisis is suspected, it needs emergency treatment without any delays, with intravenous glucocorticoids (preferably hydrocortisone), fluids, and supportive therapy. Subsequent glucocorticoid therapy should be tapered off based on clinical response. Primary care physicians in resource-limited clinical settings should successfully recognize and manage tuberculous Addison's disease.

Learning Points

1. Consider adrenal insufficiency in patients with miliary tuberculosis who present with non-specific abdominal pains, nausea, vomiting, anorexia, lethargy, hyponatremia, salt craving, dehydration, altered mental status, etc.
2. An adrenal crisis must be considered in any patient who presents in shock. The clues include persistent hypotension, hyponatremia, hyperkalemia, hypoglycemia, azotemia, and hyperpigmentation in the setting of non-specific abdominal pains, nausea, vomiting, weight loss, and lethargy.
3. An adrenal crisis is a medical emergency with a high mortality rate. When suspected, treatment must be initiated immediately with intravenous hydrocortisone, fluids, and supportive therapy. Treatment must not be delayed by the need to perform diagnostic tests.

ACKNOWLEDGEMENT

The authors acknowledge the nursing staff in the female wards and TB clinic of St. Joseph Rift Valley Hospital, Gilgil, for their help in managing this patient.

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