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Severe Hypercalcemia and Acute Kidney Injury as Unusual Presentations of Primary Adrenal Insufficiency in Schmidt Syndrome: A Case Report and Literature Review

Zineb Habbadi [1], Hiba El Aalim [1], Kaoutar Rifai [1], Hinde Iraqi [1], Mohamed El Hassan Gharbi [1]

1. Endocrinology, Diabetes, and Metabolism, Centre Hospitalier Ibn Sina, Rabat, MAR

Corresponding author: Zineb Habbadi, pr.z.habbadi@gmail.com

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Abstract

Schmidt syndrome, also known as autoimmune polyglandular syndrome type 2, is characterized by the coexistence of primary adrenal insufficiency and autoimmune thyroid disease. Although electrolyte abnormalities are common in primary adrenal insufficiency, hypercalcemia is an uncommon manifestation and is usually mild to moderate. We report the case of a 50-year-old woman with newly diagnosed autoimmune primary adrenal insufficiency and autoimmune hypothyroidism who presented with severe hypercalcemia and acute kidney injury. On admission, she had severe asthenia, nausea, vomiting, abdominal pain, weight loss, dehydration, hypotension, and generalized hyperpigmentation. Laboratory investigations revealed hyponatremia, hyperkalemia, metabolic acidosis, severe hypercalcemia, and marked renal dysfunction. The hypercalcemia was associated with a low parathyroid hormone (PTH) level, supporting a PTH-independent mechanism. Hormonal evaluation demonstrated markedly reduced serum cortisol and elevated adrenocorticotropic hormone (ACTH) levels, while positive anti-21-hydroxylase antibodies and bilateral adrenal atrophy supported the diagnosis of autoimmune primary adrenal insufficiency. Thyroid function testing revealed primary hypothyroidism with positive anti-thyroglobulin antibodies, establishing the diagnosis of Schmidt syndrome. Treatment with intravenous hydrocortisone and aggressive intravenous fluid resuscitation resulted in rapid normalization of serum calcium, electrolytes, and renal function. Levothyroxine was subsequently initiated after adequate glucocorticoid replacement had been established. This case highlights severe PTH-independent hypercalcemia and acute kidney injury as an unusual manifestation of primary adrenal insufficiency and emphasizes the importance of considering adrenal insufficiency in patients presenting with unexplained hypercalcemia, particularly when accompanied by hypotension, hyponatremia, hyperkalemia, and hyperpigmentation.

Categories: Emergency Medicine, Nephrology, Endocrinology/Diabetes/Metabolism
Keywords: acute kidney injury, addison disease, case report, hypercalcemia, schmidt syndrome

Introduction

Schmidt syndrome, also known as autoimmune polyglandular syndrome type 2, is an autoimmune endocrine disorder characterized by the coexistence of primary adrenal insufficiency and autoimmune thyroid disease, with or without type 1 diabetes mellitus [1,2]. Its estimated prevalence ranges from 1.5 to 4.5 cases per 100,000 individuals [1,3]. The associated autoimmune disorders may occur concomitantly, although one endocrine disorder is frequently diagnosed before the others [1].

Primary adrenal insufficiency usually presents with nonspecific symptoms, including fatigue, anorexia, nausea, vomiting, weight loss, abdominal pain, orthostatic dizziness, hypotension, and cutaneous or mucosal hyperpigmentation. Typical biochemical abnormalities include hyponatremia, hyperkalemia, and metabolic disturbances related to glucocorticoid and mineralocorticoid deficiency [2]. Hypercalcemia has been reported in patients with adrenal insufficiency but remains an uncommon finding. When present, it is generally mild to moderate; severe hypercalcemia is considerably less frequent [4]. Several mechanisms have been proposed, including reduced renal calcium excretion related to volume depletion and decreased glomerular filtration, increased renal calcium reabsorption, and increased bone resorption [4].

We report a case of severe parathyroid hormone (PTH)-independent hypercalcemia associated with acute kidney injury in a patient with newly diagnosed autoimmune primary adrenal insufficiency and autoimmune hypothyroidism, ultimately leading to the diagnosis of Schmidt syndrome.

Case Presentation

A 50-year-old woman with a medical history of cholecystectomy, a left ovarian cyst, and uterine fibroids was admitted to the Department of Endocrinology and Metabolic Diseases for evaluation and management of newly diagnosed primary adrenal insufficiency. Symptoms had started approximately three months before admission, with nausea, vomiting, abdominal pain, and significant weight loss. These symptoms were

accompanied by progressive generalized hyperpigmentation. Because of progressive worsening of her clinical condition, she presented to the emergency department and was subsequently admitted to our department for further evaluation and treatment.

At admission, the patient presented with severe asthenia, nausea, vomiting, and abdominal pain without impairment of consciousness. Physical examination revealed clinical signs of dehydration. Her heart rate was 114 beats per minute, and blood pressure was 90/50 mmHg in the supine position, with orthostatic hypotension. Cutaneous examination revealed generalized hyperpigmentation (Figure *1*), with slate-colored pigmentation of the oral mucosa, strongly suggestive of chronic primary adrenal insufficiency.

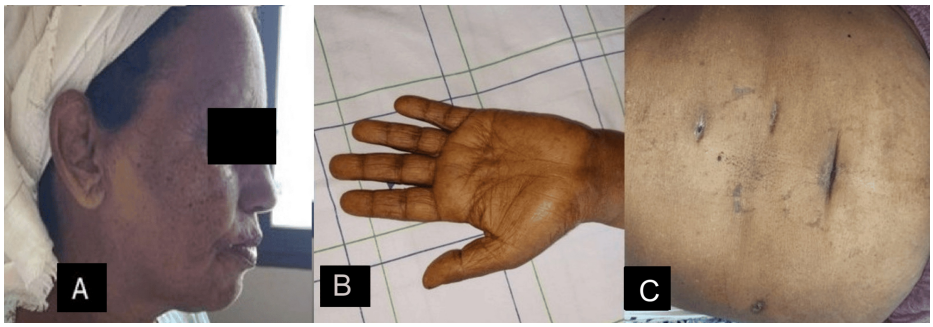


FIGURE 1: Generalized hyperpigmentation in the patient

(A) Cutaneous hyperpigmented macules involving the face; (B) Hyperpigmentation of the palmar surface of the hand; (C) Hyperpigmentation of abdominal laparoscopic surgical scars following cholecystectomy.

Initial laboratory investigations revealed hyponatremia, hyperkalemia, and metabolic acidosis with low serum bicarbonate levels. Severe hypercalcemia was also identified. The PTH concentration was inappropriately low in the context of hypercalcemia, supporting a PTH-independent mechanism in the setting of severe hypercalcemia. The patient also had severe vitamin D deficiency. Renal function was severely impaired, with markedly elevated serum urea and creatinine levels and a severely reduced estimated glomerular filtration rate (eGFR) (Table *1*). Hormonal evaluation demonstrated a low serum cortisol concentration associated with a markedly elevated adrenocorticotropic hormone (ACTH) concentration, consistent with primary adrenal insufficiency.

Parameter	Patient Value at Admission	Patient Value on Day 10	Reference Range
Sodium (mEq/L)	125	138	135–145
Potassium (mEq/L)	5.4	4.0	3.5–5.0
Bicarbonate (mmol/L)	15	23	22–31
Urea (g/L) (BUN equivalent)	1.50 (~70 mg/dL)	0.39 (~18 mg/dL)	0.15–0.45 (7–21 mg/dL)
Creatinine (mg/L)	62	9	7.5–12.5
eGFR (mL/minute/1.73 m²)	7	70	>60
Total calcium (mg/L)	153	95	84–102
Albumin (g/L)	32	32	35–52
Albumin-corrected calcium (mg/L)	161	103	84–102
Phosphate (mg/L)	34	—	25–45
PTH (pg/mL)	13.1	—	15–65
25-OH vitamin D (ng/mL)	4.7	—	30–80
Cortisol (ng/mL)	2.9	—	2.9–19.4
ACTH (pg/mL)	300	—	≤60
Anti-21-hydroxylase antibodies (U/mL)	27.7	—	<0.4
Anti-TPO antibodies (U/mL)	0.82	—	<5.61
Anti-thyroglobulin antibodies (U/mL)	6.89	—	<4.11
TSH (mIU/L)	22.34	—	0.4–4.0
FT4 (pmol/L)	7.78	—	9–19

TABLE 1: Evolution of biological parameters under treatment

eGFR: estimated glomerular filtration rate; PTH: parathyroid hormone; ACTH: adrenocorticotropic hormone; TSH: thyroid-stimulating hormone; FT4: free thyroxine; BUN: blood urea nitrogen

A computed tomography (CT) scan of the thorax, abdomen, and pelvis revealed no mediastinal lymphadenopathy, hepatosplenomegaly, or other findings suggestive of sarcoidosis or lymphoma. There was also no history of prolonged immobilization before admission.

The autoimmune origin of the adrenal insufficiency was supported by positive anti-21-hydroxylase antibodies. CT focused on the adrenal glands demonstrated bilateral adrenal atrophy. Thyroid function tests showed an elevated thyroid-stimulating hormone (TSH) concentration and a low free thyroxine (FT4) concentration. Anti-thyroglobulin antibodies were positive, whereas anti-thyroid peroxidase (anti-TPO) antibodies were negative. These findings were consistent with autoimmune primary hypothyroidism. The coexistence of autoimmune primary adrenal insufficiency and autoimmune thyroid disease established the diagnosis of Schmidt syndrome.

Because of the risk of adrenal crisis, treatment was promptly initiated with high-dose intravenous hydrocortisone hemisuccinate and aggressive intravenous crystalloid fluid resuscitation. Glucocorticoid therapy was subsequently tapered according to the patient's clinical and biochemical improvement. Maintenance treatment consisted of hydrocortisone 30 mg/day combined with fludrocortisone 0.1 mg/day. Levothyroxine replacement therapy was initiated only after adequate glucocorticoid replacement had been established and the patient had achieved clinical stabilization, at a dose of 1.6 µg/kg/day.

The patient's clinical and biochemical status improved progressively following glucocorticoid replacement and fluid resuscitation. By day 10, serum sodium had normalized, with correction of the initial hyperkalemia and metabolic acidosis. Renal function showed marked improvement, with a substantial decrease in serum creatinine and recovery of the eGFR. Serum total and albumin-corrected calcium levels also progressively decreased toward the normal range (Table *1*). At medium-term follow-up, the patient demonstrated marked improvement in her general condition, with progressive regression of the cutaneous hyperpigmentation.

Discussion

Schmidt syndrome is a form of autoimmune polyglandular syndrome type 2 characterized by the association of primary adrenal insufficiency with autoimmune thyroid disease [1,2]. Its pathogenesis involves a complex interaction between genetic susceptibility and environmental factors. Several susceptibility genes have been implicated, including *HLA-DR3*, *HLA-DR4*, *CTLA-4*, *PTPN22*, and *CD25* [5].

The clinical manifestations of primary adrenal insufficiency are frequently nonspecific and may lead to delayed diagnosis. Patients may present with fatigue, anorexia, nausea, vomiting, abdominal pain, weight loss, orthostatic dizziness, hypotension, and hyperpigmentation [2]. In the present case, the combination of chronic gastrointestinal symptoms, weight loss, hypotension, dehydration, and prominent mucocutaneous hyperpigmentation was highly suggestive of primary adrenal insufficiency.

The diagnosis is established by demonstrating cortisol deficiency in association with an elevated ACTH concentration [2]. In this patient, the cortisol concentration was markedly reduced at 2.9 ng/mL (0.29 µg/dL), while ACTH was markedly elevated at 300 pg/mL. The autoimmune etiology was further supported by positive anti-21-hydroxylase antibodies and bilateral adrenal atrophy. Autoimmune thyroiditis was confirmed by elevated TSH, low FT4, and positive anti-thyroglobulin antibodies; although anti-TPO antibodies were negative, isolated anti-thyroglobulin positivity is a well-recognized serological presentation of autoimmune thyroid disease [1,3].

The most unusual feature of this case was the presence of severe hypercalcemia (total calcium 15.3 mg/dL; corrected calcium 16.1 mg/dL). Hypercalcemia is an uncommon complication of adrenal insufficiency and has been reported in approximately 5.5% of patients with primary adrenal insufficiency [4]. In most reported cases, hypercalcemia is mild to moderate; severe hypercalcemia is considerably less common.

Several mechanisms have been proposed to explain hypercalcemia associated with adrenal insufficiency. Volume depletion resulting from glucocorticoid and mineralocorticoid deficiency reduces renal perfusion and glomerular filtration, thereby decreasing the filtered load of calcium and impairing renal calcium excretion. Increased proximal tubular reabsorption of sodium and calcium may further contribute to reduced calcium clearance. Increased bone resorption and, less frequently, increased intestinal calcium absorption have also been proposed [4].

Hypercalcemia may itself aggravate volume depletion through gastrointestinal symptoms, increased urinary water loss, and impaired renal concentrating capacity. Consequently, a vicious cycle may develop in which adrenal insufficiency causes hypovolemia and reduced renal calcium clearance, while severe hypercalcemia further worsens dehydration and renal dysfunction [4]. This mechanism may explain the coexistence of severe hypercalcemia, hypotension, and acute kidney injury observed in our patient.

In the present case, the severe hypercalcemia was associated with a PTH concentration of 13.1 pg/mL, supporting a PTH-independent mechanism. The diagnostic evaluation did not reveal clinical or radiological evidence of sarcoidosis or lymphoma, and there was no history of prolonged immobilization. The patient also had severe vitamin D deficiency rather than vitamin D excess. The rapid normalization of serum calcium following fluid resuscitation and glucocorticoid replacement further supports adrenal insufficiency as the principal contributor to the hypercalcemia.

Acute kidney injury was another prominent feature of this presentation. On admission, the patient had severe renal dysfunction, with a creatinine concentration of 62 mg/L (6.2 mg/dL) and an eGFR of 7 mL/minute/1.73 m^2. Following treatment, creatinine decreased to 9 mg/L (0.9 mg/dL), and eGFR increased to 70 mL/min/1.73 m^2 by day 10. This rapid recovery suggests that the renal impairment was predominantly functional and related to severe volume depletion and reduced renal perfusion rather than established irreversible kidney injury.

The management of hypercalcemia associated with adrenal insufficiency requires treatment of the underlying endocrine disorder in addition to restoration of intravascular volume. Intravenous fluid administration improves renal perfusion and calcium excretion, while glucocorticoid replacement corrects the underlying cortisol deficiency and contributes to normalization of calcium levels [4,6,7]. In severe or refractory hypercalcemia, particularly when accompanied by advanced renal failure or persistent hypercalcemia despite conventional treatment, hemodialysis may be considered [6,7]. In our patient, calcium normalized with fluid resuscitation and glucocorticoid replacement, and hemodialysis was therefore not required.

The coexistence of autoimmune primary adrenal insufficiency and autoimmune thyroid disease established the diagnosis of Schmidt syndrome. Importantly, glucocorticoid replacement should precede thyroid hormone replacement in patients with suspected or confirmed adrenal insufficiency. Initiating levothyroxine before correcting cortisol deficiency may increase metabolic demand and precipitate or worsen an adrenal crisis [2,3]. In our patient, levothyroxine was therefore introduced only after glucocorticoid replacement and clinical stabilization.

An additional diagnostic consideration in patients with hyponatremia is syndrome of inappropriate antidiuretic hormone (ADH) secretion. Cortisol deficiency can increase ADH secretion because cortisol normally exerts inhibitory effects on ADH release. Furthermore, hypovolemia and salt wasting associated with mineralocorticoid deficiency can provide additional stimuli for ADH secretion [2]. Thus, adrenal insufficiency may mimic the syndrome of inappropriate ADH secretion biochemically. These considerations underscore the need, in any patient presenting with hyponatremia, particularly when the clinical context is suggestive, to systematically consider adrenal insufficiency as a differential, or even coexisting, diagnosis before defaulting to a diagnosis of syndrome of inappropriate ADH secretion.

This case is clinically relevant because severe hypercalcemia can initially direct the diagnostic evaluation toward more common etiologies such as primary hyperparathyroidism, malignancy, granulomatous disease, or vitamin D-related disorders. However, the coexistence of hypercalcemia with clinical and biochemical features suggestive of primary adrenal insufficiency should prompt consideration of adrenal insufficiency. Recognition is particularly important because treatment is rapidly effective and addresses both the underlying adrenal crisis and the associated metabolic abnormalities.

The main limitation of this report is its single-case nature. Although the rapid normalization of calcium and renal function following fluid and glucocorticoid therapy supports a causal association with adrenal insufficiency, the precise mechanism responsible for the severe hypercalcemia cannot be definitively established from a single observation.

Conclusions

Severe hypercalcemia is an uncommon but potentially serious manifestation of primary adrenal insufficiency. It may coexist with profound volume depletion and acute kidney injury and can therefore contribute to a potentially life-threatening clinical presentation. Primary adrenal insufficiency should be considered in the differential diagnosis of unexplained PTH-independent hypercalcemia, particularly when hypercalcemia is associated with asthenia, gastrointestinal symptoms, hypotension, hyponatremia, hyperkalemia, dehydration, and hyperpigmentation. Early recognition and prompt initiation of glucocorticoid replacement, together with appropriate fluid resuscitation, can result in rapid clinical and biochemical recovery. In patients with autoimmune primary adrenal insufficiency and autoimmune thyroid disease, the diagnosis of Schmidt syndrome should be considered, and glucocorticoid replacement should precede thyroid hormone therapy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Zineb Habbadi, Hiba El Aalim, Kaoutar Rifai, Hinde Iraqi, Mohamed El Hassan Gharbi

Drafting of the manuscript: Zineb Habbadi, Hiba El Aalim

Critical review of the manuscript for important intellectual content: Zineb Habbadi, Kaoutar Rifai, Hinde Iraqi, Mohamed El Hassan Gharbi

Supervision: Zineb Habbadi

Disclosures

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