Symptomatic hypercalcemia in a rabies survivor underwent hemodialysis

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Abstract
Adrenal insufficiency is an uncommon and easily ignored cause among most etiologies of hypercalcemia because not all cases of adrenal insufficiency presented with hypercalcemia. In most cases of adrenal insufficiency, viral encephalitis-related panhypopituitarism is a rare complication that is sporadically encountered in previous studies. However, this complication has never been reported in rabies encephalitis because of the extremely high rate of mortality. Rapid recovery from hypercalcemia state after glucocorticoid supplement is a direct hint of adrenal insufficiency related hypercalcemia.

Key words: Rabies, encephalitis, hypercalcemia, hypopituitarism, adrenal insufficiency

INTRODUCTION
In contrast to the leading causes of hypercalcemia including primary hyperparathyroidism and malignancy-related humoral hypercalcemia, adrenal insufficiency is a relative rare etiology because not all cases presented with hypercalcemia.1 However, in patients receiving maintenance dialysis or presenting with totally loss of cortisol secretion due to severe central nervous system damage or adrenalectomy, the adrenal insufficiency related hypercalcemia are easily encountered. Here, we describe a rabies survivor who presented with refractory hypercalcemia, which led to a rare, but curable complication of rabies encephalitis-related panhypopituitarism.

CASE REPORT
A 30-year-old Taiwanese man was referred to our hospital for a suspected rabies infection. Four weeks prior to admission, a dog bit him on his left foot but the patient did not receive post-exposure prophylactic rabies vaccination. Approximately 3 weeks later to the present event, he started to feel feverish and developed headache and numbness around the wound, but still did not seek medical attention. Intermittent nausea, vomiting, and difficulty swallowing, followed by obvious hydrophobia, were also described by the patient’s family. Two days before admission, the patient was referred to a local hospital for disturbed consciousness and repetitive generalized tonic-clonic seizures. After treatment with anticonvulsants and intubation with mechanical ventilation, the
patient was transferred to our intensive care unit for further evaluation.

On admission to the intensive care unit, he was in profound shock, with rhabdomyolysis and acute kidney dysfunction. He was immediately administered fluid resuscitation and continuous veno-venous hemodialysis. Rabies virus ribonucleic acid was detected in his saliva and cerebrospinal fluid using reverse-transcriptase polymerase chain reaction performed at the Centers for Disease Control. The Milwaukee rabies protocol was initiated, which included heavy sedatives with continuous electroencephalogram monitoring and administration of muscle relaxants. In accordance with protocol suggestions, no active immunization was administered because the patient had already developed symptoms. Two weeks after admission, anti-rabies immunoglobulin G was detected in serum and cerebrospinal fluid via immunofluorescence enzyme-linked immunosorbent assay. In the fourth week after admission, the patient had survived the rabies infection but remained in a vegetative and uremic state, requiring mechanical ventilation and maintenance hemodialysis. During this period, no hypercalcemic episodes were observed, but the patient was treated for complications including hemidiaphragmatic paralysis, intermittent cardiac arrhythmia, dysautonomia with hemodynamic instability, and episodes of ventilator-associated pneumonia.

In the sixth week after admission, progressive crescendo serum calcium levels were observed; therefore, all calcium sources were removed from his diet. In addition, the patient was shifted to low-calcium dialysis treatment (0 to 2.5 mEq/L). Despite these changes, hypercalcemia persisted and 400 IU per day of calcitonin was administered intravenously. In the seventh week after admission, serum calcium levels continued to rise, accompanied by frequent cardiac arrhythmia with shortened QT intervals. Serum biochemical studies showed strikingly high ionized calcium levels (7.25 mg/dL). Further work-up revealed decreased serum levels of intact parathyroid hormone (iPTH) and 25-hydroxy vitamin D (25[OH]D) (9.10 pg/mL and 3.83 ng/mL, respectively). Serum protein electrophoresis, antineutrophil cytoplasmic antibody titers, and serial tumor markers studies were negative. Further imaging studies showed no osteolytic or osteoblastic lesions. Similarly, malignancy and chronic granuloma investigations also yielded negative results. Hormone testing showed low levels of free thyroxine (0.62 ng/dL), thyrotropin (0.06 μIU/L), diurnal cortisol (1.12 and 1.15 μg/dL), adrenocorticotropic hormone (2.32 pg/mL), 24-hour urine 17-hydroxycorticosteroids (2.50 mg/day), and 17-ketosteroids (1.40 mg/day).

Testing of other hormonal axes revealed low levels of sex hormones and insulin-like growth factor 1 (37.80 ng/mL). Brain magnetic resonance imaging showed diffuse cerebral swelling with direct compression of the pituitary gland.

The patient’s hypercalcemia was refractory to standard medical treatments including calcitonin and hemodialysis, but was responsive to intravenous hydrocortisone followed by oral cortisone (50 mg/day). The results of the biochemical studies and the excellent response to glucocorticoid therapy suggest that his hypercalcemia was most likely caused by adrenal insufficiency secondary to panhypopituitarism. The patient was finally normocalcemic with a daily physiological dose of hydrocortisone. Ten weeks after admission, the patient had recovered from the acute kidney injury and hemodialysis was suspended. Serum levels of ionized calcium, phosphate, creatinine, adrenocorticotropic hormone, and cortisol during the course of his hospitalization are summarized in Figure 1. After recovery, repeated endocrine measurements showed low levels of thyrotrpin (0.07 μIU/L), but increased levels of free thyroxine (1.12 ng/dL) and cortisol (12.24 μg/dL). Currently, the patient is stable with the aid of mechanical ventilation and supportive care in a ward.

**DISCUSSION**

Serum calcium homeostasis is controlled by the bones, kidneys, and gastrointestinal tract. About 98% of total body calcium is stored in the bones; the remaining 2% circulates throughout the body. When evaluating possible etiologies of hypercalcemia, any cause leading to increased calcium absorption from the bones or gastrointestinal tract or decreased excretion from the kidneys should be considered. Causes may include parathyroid diseases, malignancies, vitamin D overload, or any dysfunction that induces high bone turnover and renal failure. Standard clinical testing to differentiate possible causes includes detailed review of medical histories, physical examination, and measurement of serum iPTH and vitamin D levels. In hypercalcemia, the kidneys initiate reabsorption by direct action on the calcium-sensing receptor of the thick ascending limb, which has a calciiuric effect on the renal tubule, resulting in hypercalciuria. However, in patients with renal failure receiving maintenance hemodialysis, the normal calciuria compensatory pathway does not function; bone resorption and gastrointestinal tract absorption should also be considered as potential causes of persistent hypercalcemia. Common causes of hypercalcemia in patients undergoing hemodialysis include occult malignancy, especially pulmonary squamous cell carcinoma,
and hematological disease including lymphoma and bony metastases. Other etiologies include chronic granulomatous disease such as sarcoidosis, tertiary hyperparathyroidism, idiopathic hypereosinophilic syndrome, and milk-alkali syndrome.3,4 Endocrine abnormalities such as hyperthyroidism and adrenal insufficiency are less common causes of hypercalcemia (Figure 2). Increased serum 25(OH)D or 1,25(OH)₂D levels are diagnostic indicators of gastrointestinal tract absorption of calcium. However, the patient did not receive dietary excess of calcium and laboratory investigations showed relatively low serum levels of iPTH and 25(OH)D. On the basis of these findings, we consider bony resorption to be the major source of hypercalcemia in this patient.

In our patient, hypercalcemia could result from secondary adrenal insufficiency caused by panhypopituitarism, immobilization, or the recovery phase of rhabdomyolysis-related acute renal failure. Generally, hypercalcemia occurs during the diuretic phase in patients with rhabdomyolysis and acute renal failure.5 However, the patient’s hypercalcemia onset occurred in the sixth week after admission and resolved before the diuretic phase. On the basis of the laboratory test results, immobilization hypercalcemia may have led to the persistent hypercalcemia. Immobilization hypercalcemia may develop after days or months of hospitalization.6 Definitive diagnosis of immobilization-related hypercalcemia requires bone biopsy and exclusion of other factors associated with hypercalcemia. In this case, administration of corticosteroids resulted in a prompt normalization of serum calcium levels, suggesting that adrenal failure played a major role in the pathogenesis of hypercalcemia. The panhypopituitarism-related secondary adrenal insufficiency was most likely a consequence of compression of the pituitary gland by swollen brain tissue.

The mechanism of adrenal insufficiency-induced hypercalcemia remains unclear. One possible explanation is decreased circulating stanniocalcin, a paracrine hormone secreted from the adrenal gland, which could result in reduced levels of circulating calcium. Deficient adrenal hormone and decreased levels of stanniocalcin may affect skeletal calcium efflux into circulation and

Figure 1 Serum levels of creatinine, ionized calcium, inorganic phosphorus, adrenocorticotropic hormone (ACTH), and cortisol measured during hospitalization and treatment of hypercalcemia are shown. Abbreviations: (CVVHD), continuous veno-venous hemodialysis; (HD), hemodialysis.

result in hypercalcemia. In patients with hypopituitarism caused by central nervous system (CNS) infection, 10% had a single axis deficiency, while 8.3% had deficiencies in multiple axes. In addition, previous reports of viral hemorrhagic fever-related hypopituitarism have observed that most patients develop hypopituitarism during the recovery phase of acute disease and that growth hormone deficiency was the most frequent form of pituitary deficiency. Most reported cases of hypopituitarism were caused by flaviviruses (dengue, yellow fever), arenaviruses (Lassa fever), bunyaviruses (Hanta, Crimean-Congo fever), Puumala virus, and filoviruses (Ebola). Owing to the extremely rapid and fulminant course with high mortality, late disease complications are rarely reported in infections of rabies virus. Rabies is transmitted by animals carrying the virus, such as dogs, bats, and raccoons; infection generally results in acute and lethal viral encephalitis. According to the World Health Organization, more than 55,000 people die of rabies annually, with the majority of cases reported in Asia and Africa. Rabies encephalitis causes extensive destruction of the brainstem, cerebrum, and limbic nervous system. The basal ganglia and thalamus can also be damaged in later stages of the disease.

In conclusion, we suggest that progressive uncontrolled hypercalcemia should be considered an occult secondary adrenal insufficiency that could result from brain tissue injury or post-infectious sequelae in patients with severe CNS infection, particularly those undergoing hemodialysis.

Manuscript received June 2014.

REFERENCES


