



Recurrent Acute Tubular Necrosis - Rare Presentation of Hypercalcemia: A Case Report

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Abstract

Renal disorders due to hypercalcemia most commonly present as impaired concentrating ability, decreased glomerular filtration rate, calcium deposition and nephrogenic diabetes insipidus. Acute tubular necrosis is a rare manifestation of hypercalcemia. We present a case of hypercalcemia caused by excessive ingestion of calcium-based antacids resulting in ATN twice over an 8 year period. All other causes of hypercalcemia such as malignancy as well as parathyroid related hypercalcemia were ruled out. Kidney functions improved with lowering of serum calcium levels, both times. Physicians should be aware of incidents of hypercalcemia resulting in acute tubular necrosis secondary to excessive ingestion of antacids for dyspepsia.

Keywords: Hypercalcemia; Acute Tubular Necrosis; Acute Kidney Injury, Case report

Background

Acute tubular necrosis (ATN) is a rare presentation of hypercalcemia. The mechanism of ATN from high calcium is likely from direct vasoconstriction of renal arterioles, polyuria and diabetes insipidus. The direct effect of hypercalcemia on renal tubules causing ATN is not clearly understood. The complications associated with ATN are often life threatening with in-hospital survival rate of approximately 50% [1]. Current co-existence of hypercalcemia resulting in kidney injury in our patient stresses the importance of investigating ATN in cases presenting with hypercalcemia and acute renal failure for early diagnosis, timely treatment, and preventing complications.

Historically, the excessive use of calcium supplements and/or calcium-based antacids was thought to solely cause milk-alkali syndrome (also known as calcium-alkali syndrome). Patients suffering from milk-alkali syndrome present with hypercalcemia, metabolic alkalosis, and renal insufficiency [2]. Renal insufficiency secondary to hypercalcemia from Milk-Alkali syndrome most commonly present with impaired concentrating ability, decreased glomerular filtration rate (GFR), natriuresis, calcium deposition and/or nephrogenic diabetes insipidus. This case report explores a rare manifestation of hypercalcemia from Milk-Alkali syndrome resulting in ATN.

ATN is a serious Intrarenal Acute Kidney Injury (AKI) defined by the destruction of the epithelial cell lining the renal tubules. Damage to the renal tubules results in impaired filtration, blood flow, oxygenation, and may lead to acute kidney injury. Imbalances in electrolytes and waste products observed due to ATN include elevations in the fractional excretion of sodium, phosphate, urea, serum creatinine and potassium. Nephrotoxins (endogenous or exogenous) and ischemia are most likely culprits in acute renal injury. As ATN can be caused by a multitude of factors, it is important to treat ATN based on the underlying problem [1]. As seen in this case, by promptly treating hypercalcemia, improved calcium levels can lead to reversal of kidney injury. This patient experienced hypercalcemia caused by excessive ingestion of calcium-based antacids resulting in ATN twice over an eight-year period. Ninety percent of all hypercalcemia cases are due to hyperparathyroidism and malignancy, leaving 10% of cases due to other causes [3]. The incidence of milk-alkali syndrome had previously decreased with the use of Histamine-2 acid suppressing and proton pump inhibiting medications. However, recent medical literature indicates increases in patients presenting with this syndrome [4]. This may be attributable to increased physician awareness in diagnosis and subsequent reporting, but also the ease of availability in many over-the-counter antacid preparations containing calcium carbonate [4]. As

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the use of over-the-counter calcium-based antacids (i.e., TUMS, Rolaids®) become more prevalent along with accessible in today's population, it is important for clinicians to be aware of acute tubular necrosis as a potential adverse effect of hypercalcemia, especially for patients with pre-existing kidney disease.

Case Presentation

Clinical Presentation and Brief History

A 47-year old Caucasian female with past medical history of hypertension, type 2 diabetes mellitus and chronic obstructive pulmonary disease (COPD), was admitted for complaints of generalized weakness, abdominal pain, diarrhea, and confusion. The patient also reported history of taking excessive calcium-based antacids over the past several weeks for dyspepsia. Patient had been treated for similar complaints, hypercalcemia leading to acute kidney failure requiring dialysis approximately eight years prior to this admission. She has family history of hypertension; no other oncological family or genetic history was known. Patient has stable psychosocial history, with steady employment as well as living situation. She is married and lives with her spouse; she does not have any children.

Upon admission, the patient's blood pressure was 145/76 mmHg and heart rate was 80 beats per minute with no orthostatic changes temperature of 96.7°F. Physical examination was unremarkable. Initial laboratory work up revealed blood urea nitrogen (BUN) of 30mg/dl, creatinine of 3.95mg/dl, calcium of 16.3mg/dl and parathyroid hormone (iPTH) of 6pg/ml. Urine studies revealed random sodium of 71mmol/dl, creatinine of 16.2mg/dl and osmolality of 168mOsm/kg. Urine to serum creatinine ratio was less than 10 with a fraction excretion of sodium (FENa) of 13% consistent with diagnosis of acute tubular necrosis. No protein nor casts were observed on urine analysis. Renal ultrasound showed normal sized kidneys with no hydronephrosis and normal corticomedullary differentiation bilaterally.

A renal biopsy was performed and revealed the following:

- Diffuse acute tubular injury, consistent with acute tubular necrosis (Figure 1[A])
- Tubular simplification (Figure 1[B])
- Reduced brush border (Figure 1 [C])
- Normocellular glomerulus (Figure 2)

Interventions and Outcome

The patient was initially treated with intravenous (IV) normal saline, calcium-based antacids were discontinued. Later, in view of persistent hypercalcemia, calcitonin was added. Subsequently after two days, serum calcium dropped to 9.2mg/dl and patient's mental status and renal functions improved significantly. No adverse or unanticipated events were encountered.

Patient was advised to stop taking TUMS with which she complied. Subsequent monthly follow ups revealed normal serum calcium and creatinine levels. Since the incident, patient remains compliant with the treatment (discontinuation of TUMS) as evident by absence of repeat episodes of hypercalcemia. Biannual laboratory work up continues to monitor electrolytes and renal functions.

Discussion

The calcium ion is an essential regulator of several physiological processes including muscle contraction, secretory mechanisms, and neuronal excitation [5]. Hypercalcemia can result from multiple causes including malignant tumors, primary hyperparathyroidism, immobilization, ingestion of vitamins A and

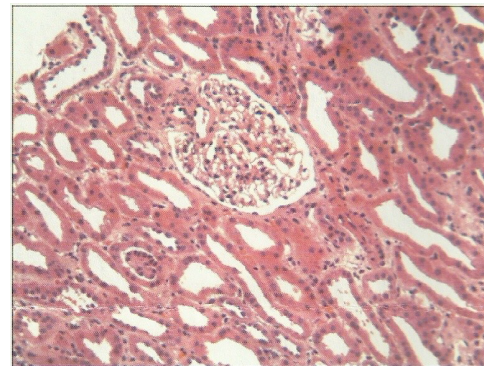


Figure 1(A): Acute tubular injury

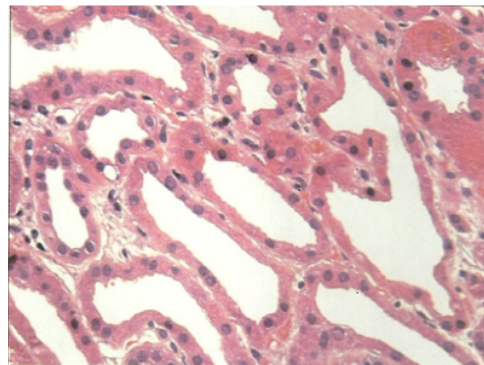


Figure 1(B): Tubular simplification

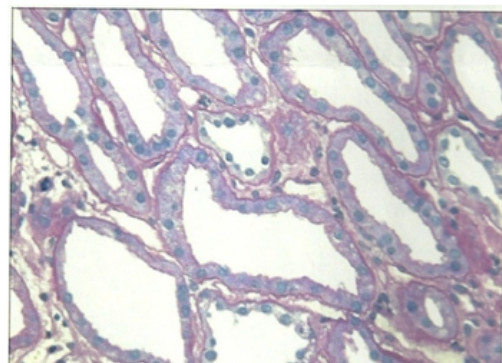


Figure 1(C): Reduced brush border

D, adverse effect of thiazide diuretics, granulomatous diseases, chronic renal failure, milk-alkali syndrome, Addison's disease, familial hypocalciuric hypercalcemia, and intrinsic bone diseases (i.e., Paget's disease) [5]. The clinical features of hypercalcemia are not specific to the etiology and are common amongst all potential causes. Patients suffering from hypercalcemia can present with dehydration, nausea, anorexia, vomiting, abdominal pain and altered mental status [5]. This patient had several of the above mentioned symptoms of hypercalcemia. The potential renal consequences of hypercalcemia are afferent arteriole vasoconstriction, decreased tubular sodium reabsorption, nephrogenic diabetes insipidus, pre-renal azotemia, nephrocalcinosis, tubulointerstitial fibrosis and ATN [6].

While current medical literature supports the hypothesis that hypercalcemia can induce acute tubular necrosis, the mechanism behind this phenomenon is not clearly defined. A study was conducted to understand the mechanism of acute calcium

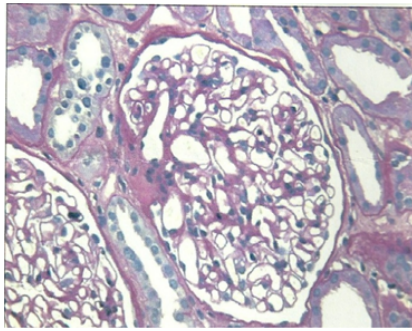


Figure 2: Normocellular glomerulus

nephrotoxicity by Ganote *et al.* Rats were infused for three hours with doses of calcium gluconate to elevate serum calcium level and were killed either immediately after infusion or after 24 hours, necrosis of proximal tubular cells was observed when serum calcium level was 16.0 mg/dl or higher [8]. Above 16.0 mg/dl, an additional 5% of renal tubular profiles contained damaged cells for each 1 mg/dl in serum calcium [8]. Initial changes were formation of granular dense bodies in mitochondria, cell swelling, rupture, and extensive mitochondrial calcification [8]. These results suggest a stronger relationship between elevated serum calcium and the development of ATN.

Currently, there are three known alterations in tubular dynamics that directly contribute to the development ATN: obstruction, back-leak and activation of tubulo-glomerular feedback [9,10]. The consistent findings of proximal tubular dilatation and distal tubular casts in human acute renal failure is indicative of obstruction to tubular fluid flow. The intraluminal casts stain strongly for Tamm-Horsfall protein, which is normally secreted by the thick ascending limb as a monomer. Conversion into a gel-like polymer is enhanced by the increased luminal sodium concentration also seen in ATN [9-11]. It is unlikely that obstruction can account for the intense dysfunction because recent human studies used forced diuresis with furosemide or mannitol did not have an impact on the survival and renal recovery rate of patients with established acute renal failure (ARF) [9].

There are several mechanisms proposed through which hypercalcemia can contribute to the development of ATN and exacerbate its symptoms. The direct vasoconstriction effects of excess calcium ions on afferent arteriolar smooth muscle cells, activation of tubule glomerular feedback in ATN dysfunction, and the symptoms of polyuria and nephrogenic diabetes insipidus caused by hypercalcemia are all proposed to contribute largely towards the renal injury observed in clinical ATN [6,9,12]. An increase in renal vascular resistance with a reduction in renal blood flow appears to result from direct vasoconstriction effects of excess calcium ions on the smooth muscle cells of the afferent arterioles [6,7]. Hypercalcemia inhibits luminal Na-K ATPase causing increased sodium load in the renal tubules. By activating the calcium-sensing receptor in the medullary thick ascending limb, the Na-K-2Cl co-transport is inhibited. This causes natriuresis and a depletion of blood volume [13]. The resulting increased delivery of sodium chloride to the macula densa due to cellular abnormalities in the ischemic proximal tubule would be expected to induce afferent arteriolar constriction via A1 adenosine receptor activation. Ultimately, the excess of calcium causes a combination of a depleted blood volume and afferent arteriolar constriction leading to a decreased GFR and an impaired renal function [9].

A retrospective study done showed that non-

hyperparathyroidism patients are more sensitive to the influence of hypercalcemia than others. This could be explained by a protective effect of parathyroid hormone (iPTH). Through a direct effect, iPTH could increase renal blood flow and GFR. Indirectly, iPTH could improve GFR via an increased tubular reabsorption of calcium, reduced hypercalciuria and diminished tubular obstruction [14].

Labraroty work up (including blood studies, urinalysis and ultrasound results) is critically important for identifying the causes of hypercalcemia and determining whether the resulting AKI is caused by pre-renal, renal or post-renal kidney injury. Specifically, performing a renal biopsy and understanding the serum BUN, serum creatinine levels, BUN to creatinine ratio, fractional excretion of sodium (FENa), urinary sodium, chloride, creatinine and urinary casts, helped identify the cause and the nature of the patient's hypercalcemia and acute kidney injury. In this patient, physical examination and vital signs on presentation were not suggestive of dehydration. Labraroty work up and ultrasound results excluded post-renal pathogenesis of ATN. The decreased BUN to creatinine ratio, increased urine sodium levels and FENa greater than 1% are noted in ATN. This suggests a possibility that in this case, hypercalcemia can cause ATN from direct effect on tubules, other than ischemic ATN from polyuria, nephrogenic diabetes insipidus and pre-renal vasoconstriction [15].

Treatment of acute hypercalcemic nephropathy should start with identifying and correcting the underlying cause. In some cases, this can mean restoring intravascular fluid volume with IV fluids and/or interrupting bone resorption with the use of bisphosphonates, calcitonin, or mithramycin. Increasing urine output by using saline and loop diuretics can be used to manage the fluid volume but should be avoided for treating ATN/AKI. Though commonly used, studies have found little to no evidence supporting the use of loop diuretics in improving patient outcomes in AKI/ATN. Some benefits of using loop diuretics include converting oliguric AKI to non-oliguric AKI, managing fluid overload and inhibiting prostaglandin dehydrogenase to improve renal flow. However, this technique has the ability to aggravate AKI by decreasing effective circulating volume, increasing the aggregation of Tamm-Horsfall protein and creating electrolyte abnormalities and metabolic alkalosis [16,17]. If hypercalcemia is promptly reversed, eventual recovery of nephron function can be expected.

However, if hypercalcemia remains chronic and persistent, various degrees of interstitial calcifications, inflammation, and sclerosis have the potential of evolving. As the duration of hypercalcemia increases, the less reversible its effects become. By waiting too long, nephrocalcinosis and chronic renal insufficiency can result.

Conclusion

The recurrent coexistence of ATN and hypercalcemia in this patient suggests that there is a deeper connection between these two conditions. The complications associated with ATN are often life threatening with an in-hospital survival rate of approximately 50% [1]. Any case presenting with hypercalcemia and acute renal failure should be investigated for ATN for early diagnosis and should receive timely treatment.

Declaration

Availability of supporting data.

Any supporting data and materials can be made available if requested.

Authors' contributions

SM: Conceived study design and manuscript creation.

SK: Research and data collection

SP: Literature research and data analysis

AM: Periodic revision as well as final editing of the article.

VD: Contributed to finalizing pathological findings.

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"Not applicable"

Conflict of Interest

The authors declare that there are no conflicts of interest regarding this publication.

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