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| RESEARCH ARTICLE

When Kidney and Calcium Speak: A Rare Presentation of Sarcoidosis: A Case Report

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| ABSTRACT

Though classic pulmonary and constitutional symptoms are present in many cases of sarcoidosis, sarcoidosis can still be clinically silent and limited to the kidneys. This case report presents a 45-year-old Saudi male who presented with non-specific symptoms in the form of fatigue only and significant laboratory findings of PTH-independent hypercalcemia as well as acute kidney injury. Screening for sarcoidosis by chest imaging demonstrated bilateral hilar lymphadenopathy consistent with early sarcoidosis, necessitating renal biopsy to confirm, which then revealed granulomatous interstitial nephritis most likely caused by renal sarcoidosis. This patient was managed mainly by oral prednisone and bisphosphonate, with partial improvement in his serum creatinine, hypercalcemia, and estimated glomerular filtration rate. This case report encourages clinicians to think beyond common causes for presentation such as hypercalcemia, particularly in the presence of acute kidney injury, to avoid irreversible complications caused by unrecognized sarcoidosis.

| KEYWORDS

Sarcoidosis, Acute Kidney Injury, Chronic Kidney Disease, Hypercalcemia, Granulomatous Interstitial Nephritis, Nephrocalcinosis, Sarcoid Granulomas, Calcium Oxalate Crystals, Chronic Kidney Disease

| ARTICLE INFORMATION

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1. Introduction

Acute Kidney Injury (AKI), previously known as acute renal failure, is a clinical syndrome characterized by a sudden decline in the kidney's ability to filter waste products, resulting in accumulation of waste products in the bloodstream. This condition is reflected by changes in laboratory values like serum creatinine, blood urea nitrogen, as well as urine output [1]. AKI is very common among hospitalized patients and is associated with higher rates of morbidity and mortality [1]. Epidemiological studies estimated that approximately 7% of all hospitalized patients develop AKI; this number rises dramatically in intensive care unit settings, reaching 67% [1]. Moreover, AKI carries an in-hospital mortality risk of 40-50%, with morality rates in intensive care units exceeding this range [1]. Importantly, since AKI causes dysregulation of the body's electrolytes and fluid balance, along with abnormal retention of nitrogenous waste, which often leads to longer hospital stays, early detection and treatment are crucial. Causes of AKI are commonly subcategorized into three categories: prerenal, renal, and postrenal. Prerenal AKI is triggered by conditions like dehydration, hemorrhage, or hypotension, where the amount of blood reaching the kidneys is significantly reduced [1]. Renal causes indicate renal tissue damage. This could occur secondary to a variety of factors such as

acute tubular necrosis (ATN) from toxins or ischemia, acute interstitial nephritis (AIN) from medications or inflammation, or the various forms of glomerulonephritis [1]. Post-renal AKI occurs due to obstruction of the urinary tract, leading to an increase in hydrostatic pressure and disrupted filtration. Such obstruction may result from various factors such as stones, malignancy, and prostate hypertrophy. Recognition of etiology is crucial and mandatory, as targeted management like fluid resuscitation, withdrawing nephrotoxins, or obstruction relief can reverse AKI and improve outcomes [1]. On the other hand, hypercalcemia is an uncommon finding in routine laboratory evaluations. Studies and surveys have observed that approximately 3-5% of in-hospital patients have high calcium levels [2], whereas in outpatient or emergency settings, the prevalence is even lower [3]. Although many cases of hypercalcemia are symptom-free or mild, significant elevations in calcium levels can cause various symptoms ("stones, bones, groans") and mandate a thorough evaluation. Overall, the two most frequent causes of hypercalcemia are hyperparathyroidism and malignancy [4]. Collectively, these two causes account for about 90% of cases [4]. Primary hyperparathyroidism is often attributed to the overproduction of parathyroid hormones by a benign parathyroid adenoma. In contrast, hypercalcemia secondary to malignancies is usually attributed to one of two causes: osteolytic metastases or cancer secretion of excessive parathyroid hormone-related peptide. There are a lot of other causes of hypercalcemia that could be considered, ranging from medication-induced to genetic syndromes. Importantly, however, hypercalcemia that is not responding to standard treatment should always be promptly evaluated and should raise the suspicion towards uncommon etiologies such as granulomatous diseases (e.g., sarcoidosis, tuberculosis) or an underlying genetic condition. Hypercalcemia's effects on the kidneys can result in AKI, with several potential mechanisms involved. One potential mechanism involves renal vasoconstriction of the afferent arteriole, resulting in decreased renal perfusion and hence a drop in the GFR [5]. Additionally, hypercalcemia can promote the occurrence of nephrogenic diabetes insipidus via down-regulation of aquaporin-2 water channels in the collecting ducts. As a result, patients would experience water reabsorption, polyuria, and subsequent volume loss leading to further decrease of renal perfusion [5]. Moreover, excess calcium can deposit in kidney tissue, causing tubulointerstitial injury and nephrocalcinosis [5]. The loop of Henle is also affected, as calcium activates the calcium-sensing receptor and boosts prostaglandin E_2 production, impairing sodium and chloride reabsorption and promoting further calcium loss in the urine and contributing to salt wasting [5]. Clinically, severe hypercalcemia can lead to an AKI, and if it is treated effectively —primarily with hydration and calcium-lowering interventions—AKI is typically reversible [5]. Sarcoidosis is an inflammatory disorder that affects different body systems. It is characterized by the development of noncaseating granulomas in affected organs [6]. While the lungs are most affected, typically seen as bilateral hilar lymphadenopathy and interstitial lung infiltrates, other affected sites include the skin, eyes, lymph nodes, liver, heart, and kidneys [6]. The exact etiology remains unclear, but a hallmark pathologic feature is aggregation of activated macrophages and T-cells into epithelioid granulomas [7]. An important metabolic effect of these granulomas is the overproduction of 1α-hydroxylase by macrophages, which convert 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D form [7]. This enhances intestinal calcium absorption, often resulting in hypercalcemia, which is observed in up to 10% of patients with sarcoidosis [7]. In addition, granulomatous tissue may produce PTH-related peptide or further metabolize vitamin D, contributing to elevated calcium levels [7]. Clinically overt renal involvement in sarcoidosis is uncommon. Although subclinical findings such as mild hypercalciuria are observed in many patients, biopsy-confirmed renal sarcoidosis is seldom encountered [8][9]. Different studies showed different values, but we can conclude that renal manifestations like stones, nephrocalcinosis, and interstitial nephritis are seen in up to 25–30% of patients when carefully evaluated [10]. Despite this, according to most reports, frank granulomatous involvement or marked AKI is documented in fewer than 1% of sarcoidosis patients [9]. If sarcoidosis affected the kidneys, it typically leads to granulomatous interstitial nephritis and calcium deposits secondary to hypercalcemia [8]. If this is unrecognized, it can lead to gradual deterioration of kidney function and renal dysfunction. Importantly, renal sarcoidosis presentation ranges from AKI to chronic kidney disease (CKD), with the risk of advancing to end-stage renal disease (ESKD) if not promptly managed. Early diagnosis is therefore critical: case reviews emphasize that delayed recognition of renal sarcoidosis often results in irreversible damage [10]. Our report underscores a rare and occult manifestation of sarcoidosis: the development of severe hypercalcemia and AKI without any overt pulmonary symptoms. Presentations like this are extremely uncommon in clinical practice. Renal sarcoidosis by itself comprises only a tiny fraction of sarcoid cases (reported around 0.3–3.5% and 0.7% in some series) [8][9]. In addition, most of the sarcoid hypercalcemia or nephritis is associated with established pulmonary disease. Very few cases in the literature document sarcoidosis presenting primarily as refractory hypercalcemia and AKI with no respiratory findings [9][11]. Our report addresses a gap in the literature, reminding physicians that unexplained AKI and hypercalcemia should prompt consideration of granulomatous disease—even without typical classic sarcoid features. Considering sarcoidosis early in the diagnostic process—including proceeding to biopsy when indicated—can prevent missed diagnoses and improve the overall prognosis.

2. Case Presentation

2.1 Patient's history and Physical Examination

This case report describes a 45-year-old Saudi male who is a non-smoker and a non-diabetic but known to be hypertensive for three years, is on amlodipine, and fully independent. He was referred after a routine health check from primary care due to elevated serum creatinine. This patient was completely asymptomatic, except for feeling 'exhausted' over the past few weeks. He described this sense of fatigue as being gradually progressive in nature. He reported no other constitutional symptoms like

subjective fever, flank pain, dysuria, hematuria, or changes in urine output. He also denied weight loss, night sweats, cough, dyspnea, chest pain, changes in bowel movement, or abdominal pain. He admitted only having mild constipation and generalized tiredness. No family history of kidney disease or any autoimmune disorder, but both parents suffered from diabetes. Other than amlodipine as antihypertensive medication, our patient denied the regular use of NSAIDs (Non-Steroidal Anti-inflammatory Drugs) or any other medications. Upon physical examination, he appeared alert and oriented with stable vital signs except for elevated blood pressure at 148\92 mmHg. No edema was identified in his extremities, skin rash or erythema nodosum. Cardiovascular, respiratory, and abdominal examinations were unremarkable. Despite examinations by different physicians, no lymph nodes were detected. Noteworthy, his joints showed no signs of inflammation, like tenderness, redness or swelling.

2.2 Investigations

Extensive lab work was done for this patient (Table 1), as well as urine analysis (Table 2). The patient's estimated glomerular filtration rate of approximately 35mL\min\1.73^2 and elevated serum creatinine of 2.8 mg\dL were consistent with chronic kidney disease stage 3, while the presence of hypercalcemia despite low to normal parathyroid hormone levels suggested PTH-independent hypercalcemia. While normal serum angiotensin converting enzyme argued against sarcoidosis, other evidence like raised inflammatory markers and PTH-independent hypercalcemia indicated screening for sarcoidosis by chest X-ray, which then exposed findings suggestive of bilateral hilar lymphadenopathy without any lung infiltrates, which are typical findings of early sarcoidosis, consistent with stage 1 of sarcoidosis. For better assessment and visualization of lymphadenopathy, a chest CT had to be conducted, which demonstrated non-necrotic, non-calcified well-defined bilateral hilar and mediastinal lymph nodes with no masses, excluding any potential malignancy. To evaluate the morphology of the kidneys, renal ultrasonography was also ordered, which revealed normal kidney size and absence of hydronephrosis and stones, but there was a mild increase in cortical echogenicity. These ultrasonographic findings are compatible with interstitial nephritis and were enough to exclude obstructive causes. The absence of heavy proteinuria in urine analysis also supported the possibility of interstitial disease over glomerular disease. To further confirm the diagnosis, renal biopsy was the ideal next step, which was done successfully without any complications and brought about the significant findings of multiple non-caseating granulomas and mild lymphocytic infiltrate. Renal biopsy excluded any vasculitis, presence of acid-fast bacilli, or immune deposits (by immunofluorescence). This whole picture was consistent with granulomatous interstitial nephritis, most likely caused by sarcoidosis.

Test	Result	Normal Range
Sodium	138 mmol\L	135-145
Potassium	4.5 mmol\L	3.5-5.0
Chloride	102 mmol\L	98-107
Bicarbonate	19 mmol\L	22-29
BUN	46 mg\dL	7-20
Creatinine	2.8 mg\dL	0.5-0.9
eGFR	35mL\min\1.73^2	>90
Fasting glucose	90 mg\dL	70-100
Calcium	11.5 mg\dL	8.5-10.2
PTH	12pg\mL	10-65
rPTH	Not available	-
25-OH Vitamin D	18 ng\mL	30-100
1,25-Dihydroxy Vitamin D	90 pg\mL	20-60
Serum ACE	40 U\l	8-52
Phosphate	2.7 mg\dL	2.5-4.5
Hemoglobin	11 g\dL	12-16
WBC	7x10^9\L	4-10
Platelets	250x10^9\L	150-400
MCV	88 fL	80-100
ESR\CEP	Mildly elevated	-
LFTs	Normal	-

Table 1: results of lab work.

Parameter	Result	Normal description
Color	Yellow	Yellow
Appearance	Clear	Clear
Specific Gravity	1.015	1.005-1.030
pH	6.0	4.5-8
Protein	+1	Negative or trace
Glucose	Negative	Negative
Ketones	Negative	Negative
RBCs	None	None or few
WBCs	0-2\HPF	0-5\HPF
Bacteria	-	None
Crystals	-	None or occasional
Casts	None	None
Nitrites	Negative	Negative
Leukocyte Esterase	Negative	Negative

Table 2: results of urine analysis.

2.3 Management course

This patient was electively admitted to the medical ward for close monitoring, further workup and management. To enhance renal excretion of calcium, immediate intravenous normal saline was started with a rate of 200 mL\hour, while monitoring electrolytes and urine output. As first-line therapy for hypercalcemia, an oral dose of 40mg\day prednisone was prescribed to this patient, but since serum creatinine did not stabilize within one week of hydration and steroids, and his calcium dropped to 11 mg\dL but stayed above normal ranges, bisphosphonate therapy was initiated in the form of a Pamidronate 60mg IV infusion over 4 hours, administered once while continuing prednisone 40 mg daily. On day 10, serum calcium dropped to 10.1 mg\dL and serum creatinine stabilized at 2.3 mg\dl. Our patient reported improvement in his fatigue. From this moment, the plan continued with the prednisone for 6 more weeks before slow tapering while monitoring kidney functions, serum calcium, and electrolytes every 2 weeks. During admission, elevated blood pressure was managed by cautious use of a low dose of ACE inhibitors in the form of lisinopril 10 mg daily, considering their renal benefits in the reduction of hyperfiltration injury. This patient was advised against use of calcium and vitamin D supplements until serum calcium levels are sustained within normal limits. Eventually, the outcome after 3 months included a serum calcium at 9.7 mg\dL, serum creatinine at 1.5 mg\dL and an estimated glomerular filtration rate of 50mL\min\1.73m^2.

3. Discussion

This case highlights exactly why sarcoidosis is challenging to identify when it is renal limited. As a matter of fact, we do not have any definitive diagnostic criteria for sarcoidosis, and this patient did not come with typical manifestations, like cough, skin lesions, constitutional symptoms, or uveitis, but came with a nonspecific presentation in the form of fatigue only. [14] While kidney function tests reflected renal impairment, failure of creatinine and blood urea to recover in response to fluid therapy has already diminished the probability of a pre-renal cause, and renal ultrasonography completely excluded post-renal causes, leaving intrinsic renal disease as the only possibility [1][3]. Usually, in glomerular diseases where the glomerular membrane is defective as a final pathophysiological outcome, heavy proteinuria is observed, as the entire filtration barrier is compromised [1][3]. This was not the case with this patient, whose urine analysis showed neither heavy proteinuria nor active urine sediment, which was later supported by 24-hour urine analysis [1][3]. The absence of heavy proteinuria hints towards a tubular disease rather than a glomerular one, correlating with the renal ultrasonography findings [3]. Through medication history is a must in any unexplained renal impairment, as acute interstitial nephritis represents an underdiagnosed cause of acute kidney injury in hospital as well as non-hospital settings, and it is mostly caused by medications like antibiotics or antiepileptics [1][3]. Yet, when discussing the context of acute kidney injury and hypercalcemia occurring simultaneously, it is always crucial to rule out the overuse of vitamin D and multiple myeloma, which both were unlikely in this case [4]. And even though pulmonary symptoms were absent, imaging findings from chest X-rays and chest CT served us big hints for the diagnosis of sarcoidosis, highlighting the importance of imaging as screening tools for a pathology like sarcoidosis [6]. In many cases of sarcoidosis, angiotensin-converting enzyme is found to be elevated, but not in this case, adding to the diagnostic challenges and highlighting that normal angiotensin-converting enzyme does not exclude sarcoidosis [6]. Noteworthy, 25-hydroxyvitamin D is a form of vitamin D that reflects its stores in our body, while 1,25-dihydroxyvitamin D is the biologically active form and is produced mainly by the kidney after activation of 25-hydroxyvitamin D by the renal enzyme 1-alpha-hydroxylase [6]. In sarcoidosis, macrophages within granulomas can express this enzyme, liberating high levels of activated vitamin D, and because granulomatous 1-alpha-hydroxlase is not regulated by any negative feedback from parathyroid hormone or calcium, it continuously converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D up to consumption of 25-OH D. This paradox explains the laboratory test results for vitamin D in this case and supports the diagnosis of sarcoidosis [6]. Additionally, this case reinforces the role of renal biopsy

to find the root cause for renal impairments when clinical and lab data are insufficient or vague [12]. Despite lack of studies in regard of appropriate therapeutic options in such cases, prednisone is known to improve both hypercalcemia and granulomatous inflammation and is sufficient most of the time in managing hypercalcemia-related acute kidney injury, but if it fails, escalation to bisphosphonate is necessary [3]. Unfortunately, bisphosphonate is a nephrotoxic agent that requires balancing the risk of nephrotoxicity versus the benefits of improving hypercalcemia [3]. Relapses after glucocorticoid discontinuation remain a major concern, being seen in up to 30-40% of patients suffering from renal sarcoidosis, but they are generally responsive to re-introduction of glucocorticoids [13]. Median follow-up of 24 months demonstrated that most patients respond well to treatment, but residual and permanent renal dysfunction persisted in most – likely owing to the delayed recognition and initiation of therapy, emphasizing how early recognition is vital to prevent the irreversible outcomes like interstitial fibrosis and glomerulosclerosis [14].

4. Conclusion

This case is so unique because it demonstrates that sarcoidosis can indeed present without classic pulmonary or systemic symptoms, highlighting the importance of considering sarcoidosis in any unexplained acute kidney injury with hypercalcemia, underlining also the rarity of isolated renal sarcoidosis. This case is a reminder that granulomatous disease can be silent. Finally, the irreversible dangers of delayed diagnosis of renal sarcoidosis can only be prevented by early recognition, which itself requires thinking beyond common causes of presentations such as hypercalcemia.

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