# Sarcoidosis-Associated Hypercalcemia in a Patient with End-Stage Renal Disease

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Patients with end-stage renal disease (ESRD) usually have hypocalcemia; in context of the current treatments for renal osteodystrophy, however, it is not unusual for these patients to develop hypercalcemia. Current treatments for renal osteodystrophy include suppression of parathyroid hormone secretion by agents such as vitamin D analogues and calcimimetic agents and inhibition of intestinal phosphate absorption by phosphate binders such as sevelamer and calcium-based compounds.

Hypercalcemia in ESRD may have several different causes, including vitamin D and calcium supplementation, and diagnosing the underlying etiology can be challenging. Hypercalcemia is particularly harmful for patients with ESRD because these patients often have associated hyperphosphatemia, which can result in precipitation of calcium phosphate salts and deposition in different organs. This deposition may lead to worsening of renal function, accelerated atherosclerosis, valvular heart disease, metastatic calcification, and/or calciphylaxis. Thus, hypercalcemia in patients with renal failure should be aggressively managed and every effort made to identify and treat the underlying etiology. In addition to the causes noted previously, hypercalcemia commonly occurs in patients with sarcoidosis; these patients respond well to treatment with corticosteroids.[1] The following case report and discussion focuses on a patient with ESRD who presents with sarcoidosis-related hypercalcemia.

## CASE PRESENTATION

### Initial Presentation

A 31-year-old white man with hemodialysis-dependent ESRD secondary to diabetic nephropathy visited his nephrologist for a routine follow-up examination. Laboratory studies revealed unexplained hypercalcemia with an ionized calcium level of 1.49 mmol/L (normal, 1.1 to 1.3 mmol/L). The patient was not taking any calcium-based or other type of phosphate binders, magnesium, or vitamin D or vitamin A analogue supplements. Dietary review did not indicate any excessive ingestion of milk or other dairy products. Physical examination was unremarkable. Diagnostic work-up revealed a suppressed serum parathyroid hormone (PTH) level. Additional studies revealed a thyroid-stimulating hormone of 7.93 μIU/mL (normal, 0.35–5.50), a total $T_4$ of 5.6 μg/dL (normal, 4.5–11.5), and a free $T_4$ of 1.04 μg/dL (normal 0.71-1.85). PTH-related peptide testing was negative, and the results of serum protein electrophoresis were normal. Urine testing for Bence-Jones protein was negative. A follow-up appointment was scheduled.

### 6 Weeks Later

The patient presented to the clinic 6 weeks later with a 1-week history of lethargy, weakness, nausea, and vomiting. Results of laboratory studies performed at this time are noted in **Table 1**. There were no changes on electrocardiogram that reflected hypercalcemia. Clinical suspicion of malignancy causing hypercalcemia was raised. A computed tomography scan of the abdomen revealed splenomegaly with multiple punctate lesions (**Figure 1**). A confirmatory magnetic resonance image of the abdomen showed multiple small areas of decreased signal intensity in the spleen and liver.

### Treatment and Outcome

The patient subsequently underwent a diagnostic laparotomy with splenectomy and liver biopsy. Pathology results revealed noncaseating granulomas in the spleen (**Figure 2**) and liver. The specimens stained positive for angiotensin-converting enzyme (**Figure 3**). These features, in addition to a negative Ziehl-Nielsen stain for acid-fast bacilli, confirmed the diagnosis of sarcoidosis.

The patient was started on corticosteroids, and within 2 weeks his symptoms improved and his serum calcium level decreased to normal limits.

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**Table 1.** Laboratory Values for Case Patient

| Parameter | Value | Normal Range |
|---|---|---|
| Serum creatinine (mg/dL) | 6.8 | 0.7–1.5 |
| Blood urea nitrogen (mg/dL) | 66 | 10–20 |
| Serum calcium (mg/dL) | 12.7 | 8.3–10.5 |
| Ionized calcium (mmol/L) | 1.8 | 1.1–1.3 |
| Serum phosphorus (mg/dL) | 7.2 | 2.5–4.8 |
| Serum 1,25-dihydroxyvitamin D level (pg/mL) | 41 | 18–62 |
| Serum angiotensin-converting enzyme (U/L) | 79 | 20–60 |

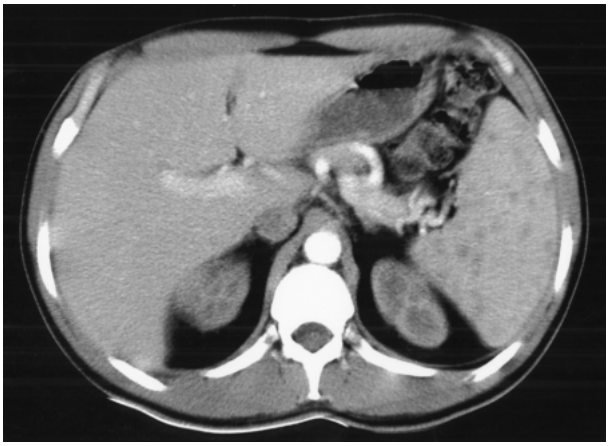

**Figure 1.** Computed tomography scan of the abdomen of the case patient reveals splenomegaly with multiple punctate lesions.

## DISCUSSION

### Hypercalcemia in ESRD

Hypercalcemia in patients with chronic renal disease is unusual, but its incidence is higher after renal transplantation, when up to 30% of patients develop hypercalcemia.[2] Abnormal calcium homeostasis is a fundamental aspect of ESRD. Low vitamin D levels, hyperphosphatemia, and skeletal resistance to PTH in these patients lead to hypocalcemia that, if untreated, can cause renal osteodystrophy. Hypocalcemia can be effectively prevented by treatment with vitamin D and calcium supplementation as well as with phosphate binders. In fact, the incidence of hypercalcemia in patients with ESRD has increased in recent years because of overtreatment with these agents.[3] Clinicians must thus strike a balance in the treatment of a patient with calcium abnormalities and ESRD—undertreatment can cause hyperparathyroidism and subsequent renal bone disease; overtreatment can cause hypercalcemia, extraskeletal calcification, and calciphylaxis. Patients may also develop adynamic bone disease as a consequence of aggressive treatment of hyperparathyroidism.[4]

In addition to calcium and vitamin D supplementation, the numerous causes of hypercalcemia in ESRD include tertiary hyperparathyroidism, aluminum toxicity, vitamin A toxicity, high calcium level in dialysate, thiazide diuretics, and prolonged immobilization (**Table 2**). In addition, ESRD patients may develop intercurrent illnesses, such as multiple myeloma, lymphoma, and granulomatous diseases, any of which alone can cause an elevated serum calcium level. In such cases, it may be difficult to discern whether the pre-existing renal disease or the superimposed illness is causing the hypercalcemia.

The clinical features of hypercalcemia depend on the serum calcium level. Mild hypercalcemia can be totally asymptomatic and only detected incidentally on a routine blood test. When calcium levels rise above 11.5 mg/dL, patients may develop symptoms of nausea, vomiting, fatigue, somnolence, lack of concentration, and mental confusion. Some of these symptoms may be attributed to ESRD and thus lead to a delay in the diagnosis of hypercalcemia until the patient develops end-organ damage in the form of extraskeletal calcification and/or calciphylaxis.

Patients with ESRD have associated hyperphosphatemia; hypercalcemia in these patients can lead to formation of calcium phosphate salts that can precipitate in various organs (including the arterial walls, heart, lungs, and subcutaneous tissues) and cause ischemia and/or organ impairment. Calciphylaxis is a rare but serious disorder characterized by calcification of arteries with resultant tissue ischemia. The pathogenesis remains largely unclear; however, high production of calcium phosphate salts seems to be an important factor in the development of calciphylaxis and its incidence increases greatly when the serum calcium-phosphorus product is greater than 70 mg/dL.[5]

Hypercalcemia, such as that caused by sarcoidosis, can cause progression of renal disease that in turn leads to further elevation of serum calcium, setting into motion a downward spiral. As in other tissues, calcium phosphate salts can be deposited in the kidney, causing further damage. Additionally, hypercalcemia can be detrimental to kidneys by causing vasoconstriction of its afferent arterioles, which causes decreased blood flow and reduced glomerular filtration rate. Finding the underlying etiology of hypercalcemia and maintaining the calcium level within normal limits may reduce this progression of renal disease.

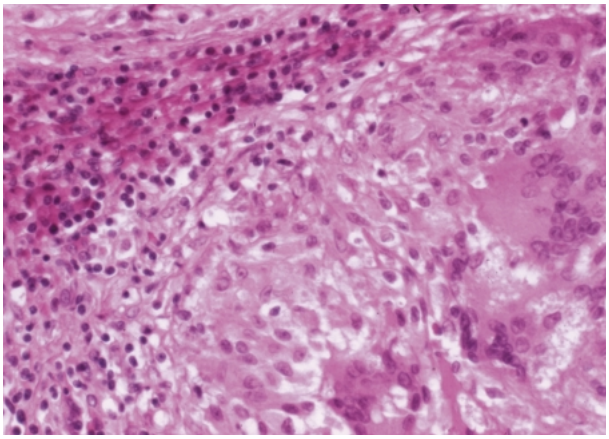

**Figure 2.** Hematoxylin-eosin stain of spleen section of case patient showing noncaseating granulomatous inflammation. Magnification ×300.

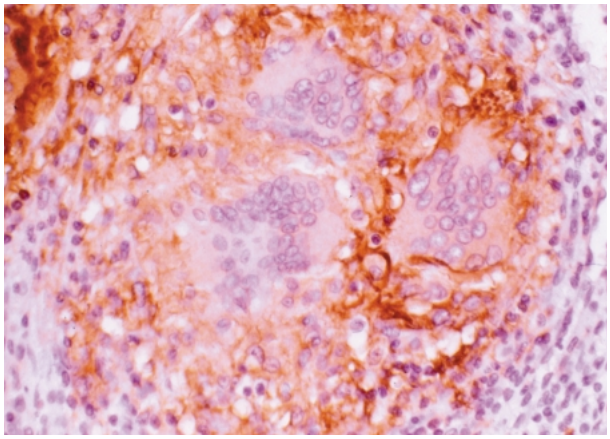

**Figure 3.** A spleen section of the case patient demonstrates positive staining for angiotensin-converting enzyme. Magnification ×400.

**Table 2.** Causes of Hypercalcemia in End-Stage Renal Disease

| |
|---|
| Calcium and vitamin D supplementation |
| Tertiary hyperparathyroidism |
| Aluminum intoxication |
| High calcium level in dialysate |
| Patient immobilization |
| Thiazide diuretics |
| Vitamin A intoxication |
| Concomitant disease |
| Malignancy |
| Granulomatous diseases |
| Tuberculosis |
| Sarcoidosis |
| Disseminated candidiasis |
| Leprosy |
| Coccidioidomycosis |
| Histoplasmosis |
| Berylliosis |
| Eosinophilic granuloma |
| Primary hyperparathyroidism |
| Hyperthyroidism |

### Management of ESRD-Associated Hypercalcemia Based on Etiology

Most patients with ESRD take calcium and vitamin D supplements, which is perhaps the most common cause of hypercalcemia in these patients. Before starting a diagnostic work-up, vitamin D and calcium supplements should be stopped and the calcium level checked after a few weeks. In patients receiving hemodialysis, a high calcium level in the dialysate can lead to hypercalcemia, which usually responds to a change in calcium concentration in the dialysate fluid.[6]

**Tertiary hyperparathyroidism.** Persistent hypercalcemia should raise the suspicion of tertiary hyperparathyroidism. Chronically low calcium and vitamin D levels have a stimulatory effect on the parathyroid gland,[7] which can lead to formation of an autonomous nodule superimposed on diffuse hyperplasia. In ESRD, a PTH level 2 to 3 times above the normal range is not uncommon; however, a very high serum PTH level in association with hypercalcemia should raise clinical suspicion of tertiary hyperparathyroidism. Most of these patients eventually require parathyroidectomy, although immediate treatment with calcimimetic agents may suffice.[8]

**Aluminum toxicity.** Aluminum toxicity resulting from exposure to aluminum-containing dialysate or intake of phosphate binders that contain aluminum is another cause of hypercalcemia in patients with ESRD.[9] Aluminum inhibits the uptake of calcium by bone, which leads to elevated serum calcium levels, especially in patients taking calcium and vitamin D supplements.[9] In these patients, withdrawal of aluminum, calcium, and vitamin D supplementation usually corrects the abnormality. In severe and resistant cases of aluminum toxicity, aluminum deposits can also be removed by treatment with desferrioxamine.[10]

**Vitamin A toxicity.** Patients with ESRD are at risk of developing hypervitaminosis A if they consume nutritional supplements containing this vitamin. The exact mechanism for hypercalcemia is unclear, but it is suspected to result from release of calcium from bone.

There is also some evidence to suggest that vitamin A stimulates PTH secretion.[11] Because patients may fail to provide history of vitamin A supplement intake, physicians should specifically ask for this in patients with ESRD who present with hypercalcemia. Most patients respond to cessation of vitamin A supplementation.

**Immobilization.** Prolonged immobilization can result in hypercalcemia due to increased bone resorption. Such hypercalcemia is characterized by low levels of PTH and 1,25-dihydroxyvitamin D. Hypercalcemia usually reverses after resumption of activity; however, bisphosphonates have been used for treatment in severe cases.[12]

**Malignancy-associated hypercalcemia.** Malignancy-associated hypercalcemia can result from osteolytic lesions, release of PTH-related hormone by malignant cells, or excessive formation of 1,25-dihydroxyvitamin D. Metastatic disease can be diagnosed by imaging studies, including radiography and bone scan. If these studies are negative, the serum level of PTH-related hormone should be measured. Elevated levels of this hormone points towards underlying malignancy, although the sensitivity and specificity of this test is low. PTH-related hormone is elevated in only 30% to 50% of patients with malignancy and high serum levels can be found in other diseases, including sarcoidosis.[13]

**Granulomatous diseases.** Granulomatous diseases that may cause hypercalcemia include tuberculosis, sarcoidosis, disseminated candidiasis, leprosy, coccidioidomycosis, histoplasmosis, berylliosis, and eosinophilic granuloma. Patients usually have symptoms of the underlying disease, although diseases such as sarcoidosis may be asymptomatic and pose a diagnostic challenge. When other causes of hypercalcemia have been excluded, investigations should be directed to finding these underlying etiologies.

One of the clues to the presence of the granulomatous diseases is the serum level of 1,25-dihydroxyvitamin D. The levels of 1,25-dihydroxyvitamin D are normally low in ESRD because the kidneys are involved in hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D; however, if the levels of 1,25-dihydroxyvitamin D are high and the patient is not receiving vitamin D supplements, then extrarenal production of 1,25-dihydroxyvitamin D by a granulomatous disease should be suspected.[1]

In addition, the level of serum angiotensin-converting enzyme is elevated in up to 75% of patients with untreated sarcoidosis and may aid in diagnosing this disease.[14] In most cases of granulomatous disease, tissue biopsy is needed to confirm the diagnosis. Hypercalcemia in granulomatous disease can be corrected by treating the underlying cause and in sarcoidosis specifically, by the use of systemic corticosteroids. Further discussion of sarcoidosis as a cause of hypercalcemia is presented later in this article.

**Serum phosphorus level.** Finally, the serum phosphorus level plays an important role in the precipitation of calcium and development of secondary hyperparathyroidism. A normal level of serum phosphorus should therefore be maintained by the use of intestinal phosphate binders, limitation of phosphorus intake, and dialysis. Daily phosphorus intake should be limited to 800 to 1000 mg, and the serum level monitored regularly to maintain a value between 3 to 5 mg/dL.

### Sarcoidosis-Associated Hypercalcemia

Sarcoidosis is a systemic granulomatous disease that has intrigued clinicians since it was first described by English physician Jonathan Hutchinson in the late 19th century. The etiology, prevalence, and annual incidence of this disease, however, remain largely unknown. Sarcoidosis commonly involves the lungs; in approximately 50% of cases, the disease is detected incidentally on chest radiography. The spleen is the second most commonly involved organ in sarcoidosis, although any organ of the body can be involved.[15]

The reported incidence of hypercalcemia in sarcoidosis varies from 2% to 63%.[16,17] The pathophysiology of sarcoidosis-associated hypercalcemia is not fully understood. Many theories have been proposed, including hyperabsorption of calcium by the small intestine, increased bone resorption, and production of PTH-related hormone.[13,18] The mechanism of action in sarcoidosis most commonly thought to cause hypercalcemia is dysregulated production of vitamin D by activated macrophages.[1]

The kidneys are affected in up to 20% of patients with sarcoidosis, although the disease only occasionally leads to clinically relevant renal dysfunction and rarely results in ESRD.[15] ESRD is usually caused by the hypercalcemia and hypercalciuria that accompany sarcoidosis; however, ESRD can also result from granulomatous interstitial nephritis, glomerular disease, and obstructive uropathy associated with sarcoidosis.[19,20] Most patients who clinically manifest sarcoidosis-associated renal disease have clear evidence of diffuse active sarcoidosis. Rarely, a patient may present with isolated elevation of serum creatinine without systemic manifestations of sarcoidosis.[21] In such cases, a kidney biopsy may help to establish the diagnosis.

Sarcoidosis-associated hypercalcemia is effectively treated by corticosteroids. The mechanism of action of these drugs is to block synthesis of 1,25-dihydroxyvitamin D in sarcoid tissue. Corticosteroids may correct

hypercalcemia within 3 to 5 days of treatment. Chloroquine, hydrochloroquine, and ketoconazole are other drugs that have been used for treatment of hypercalcemia in this setting.[22,23]

## CONCLUSION

Calcium metabolism in patients with ESRD is complex. Concomitant illness associated with an elevation in serum calcium level can further complicate the clinical picture making it difficult to diagnosis the underlying disease and manage hypercalcemia in these patients. Sarcoidosis is a relatively uncommon disease but commonly causes hypercalcemia. Patients for whom sarcoidosis is identified as the cause of hypercalcemia respond well to corticosteroid treatment. **HP**

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