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Asymptomatic Hypercalcemia and Acute Kidney Injury as Presenting Manifestation of Sarcoidosis: A Case Report

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Abstract Acute renal failure is rarely associated with the usual presentations of sarcoidosis. Sarcoidosis is associated with hypercalcemia and presents with granulomas within other organs, usually the lungs [1]. We present a case of acute renal failure with hypercalcemia in an African American female patient who was eventually diagnosed with sarcoidosis.

Keywords: *sarcoidosis, acute renal failure, hypercalcemia*

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1. Introduction

Sarcoidosis is a chronic systemic disease marked by the formation of non-caseating granulomas within various organs [1]. It affects people of all racial and ethnic backgrounds, and usually manifests between 20 to 39 years of age [2]. Annual incidence among African Americans is three-times higher than White Americans, and African Americans experience higher rates of mortality and morbidity due to sarcoidosis [2].

Hypercalcemia is seen in 10 to 20 percent of patients with sarcoidosis [3]. It is the presenting manifestation in less than 5 percent of patients [4]. Among patients with sarcoidosis, hypercalcemia is more commonly found in the Caucasian population compared to the African American population [5].

Renal involvement in sarcoidosis ranges from 0.7 to 48 percent of cases [6,7]. Acute renal failure is rarely the presenting manifestation of sarcoidosis [8]. When present, renal impairment manifests most commonly as granulomatous interstitial nephritis (GIN), but can also manifest as non-granulomatous tubulointerstitial nephritis, retroperitoneal sarcoidosis with obstructive uropathy, or many of the nephrotic disorders [9].

2. Case

Our patient was a 53-year-old African American female with a prior medical history of chronic anemia, prediabetes, hyperlipidemia, and a benign right breast cyst. She presented to the emergency department due to severe hypercalcemia noted on routine labs following her annual wellness exam. On review of systems, she endorsed polyuria and polydipsia. Her vital signs were within normal limits. A physical exam was unremarkable.

Initial labs taken in the emergency department are summarized in Table 1. Notably, they revealed hypercalcemia (Ca 14.4 mg/dL), mild anemia (Hgb 11.0 gm/dL), and acute kidney injury (BUN 20 mg/dL, creatinine 2.30 mg/dL). She was started on IV fluids and admitted to the inpatient unit.

Table 1. CBC and CMP Laboratory Results in the Emergency Dept

WBC	7.0 thousand/uL	4-10 thousand/uL
Hgb	11.0 gm/dL	11.7-15.7 gm/dL
Hct	33.1%	35-46%
Platelets	254 thousand/uL	150-400 thousand/uL
Sodium	139 mmol/L	136-145 mmol/L
Potassium	3.4 mmol/L	3.5-5.1 mmol/L
Chloride	103 mmol/L	98-107 mmol/L
CO2	27/0 mmol/L	22-29 mmol/L
Glucose	113 mg/dL	70-105 mg/dL
BUN	20 mg/dL	8-25 mg/dL
Creatinine	2.30 mg/dL	0.6-1.1 mg/dL
Calcium	14.4 mg/dL	8.4-10.5 mg/dL
Magnesium	2.2 mg/dL	1.6-2.6 mg/dL
Total Protein	7.9 gm/dL	6.5-8.4 gm/dL
Albumin	4.2 gm/dL	3.5-5.0 gm/dL
AST	36 Units/L	0-55 Units/L
ALT	32 Units/L	5-34 Units/L
Alkaline Phosphatase	101 Units/L	40-150 Units/L

Table 2. Laboratory Results to Determine Etiology of Hypercalcemia

Parathyroid Hormone	9.1 pg/mL	10-55 pg/mL
Parathyroid Hormone Related Peptide	12.0 pg/mL	undetectable
25-hydroxy Vit D	17.3 ng/mL	>30 ng/mL
1,25-dihydroxy Vit D	182 pg/mL	20-76 pg/mL
Angiotensin Converting Enzyme	286 Units/L	<40 Units/L
ANA	Positive	Negative
Anti-dsDNA	20 Int Unit/mL	Negative
Anti-Jo-1	Negative	Negative
Anti-Scl-70	Positive	Negative
Anti-Smith	Negative	Negative
Anti-SSA/Ro	Negative	Negative
Anti-SSB/La	Negative	Negative
Anti-U1 RNP	Negative	Negative
CA 125	32.2	<35
CA 15-3	18.8	<30
CA 19-9	6.06	<35
CEA	1.21	0-2.5
Cocci Ab to F Ag (IgG)	Negative	Negative
Cocci Ab to TP Ag (IgM)	Negative	Negative
QuantiFERON TB	Negative	Negative

A series of lab tests were done to determine the underlying etiology of her hypercalcemia. The results are summarized in Table 2. Notably, parathyroid hormone was suppressed (PTH 6.6 pg/mL), parathyroid hormone related peptide was high (PTHrP 12.0 pg/mL), 25-hydroxy Vit D was decreased (25-(OH)D 17.3 ng/mL), 1,25-dihydroxy Vit D was elevated (1,25-2(OH)D 182 pg/mL), and angiotensin converting enzyme was elevated (ACE 286 Units/L). An antibody screen revealed a positive ANA and a positive Anti-Scl-70. QuantiFERON TB test and Coccidioides tests were both negative. Serum protein electrophoresis and urine protein electrophoresis were both normal.

Initial imaging included a bilateral renal ultrasound that showed an incidental non-obstructing right renal calculus with no other evidence of acute findings. Once her renal function improved, a contrast CT chest-abdomen-pelvis was performed and showed mediastinal, abdominal, and retroperitoneal lymphadenopathy, the largest measuring up to 2 x 2.2 cm (Figure 1). Bilateral innumerable perilymphatic interstitial pulmonary nodules were also noted in the upper lobes (Figure 2). Her lymph nodes were not amenable to biopsy by interventional radiology. Instead, she underwent mediastinoscopy with mediastinal lymph node biopsy, which showed non-caseating granulomas consistent with sarcoidosis.

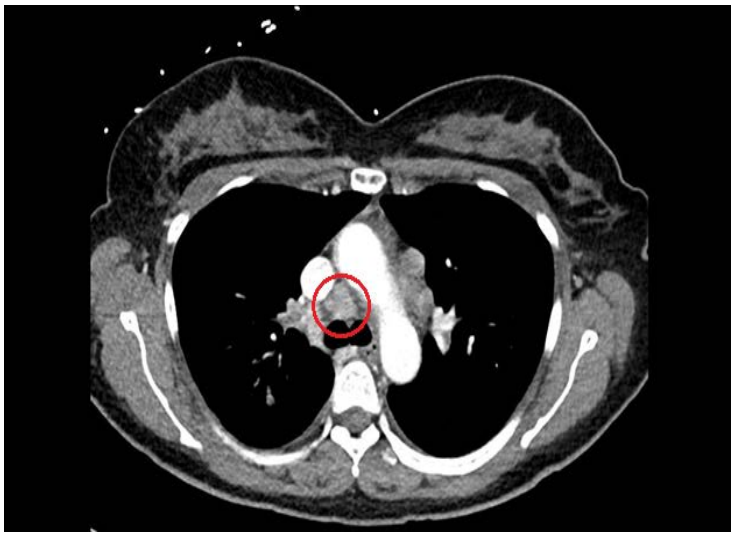

Figure 1. Chest CT images. Contrast CT showing pre-carinal lymphadenopathy measuring 2.0 x 2.2 cm, marked by the red circle

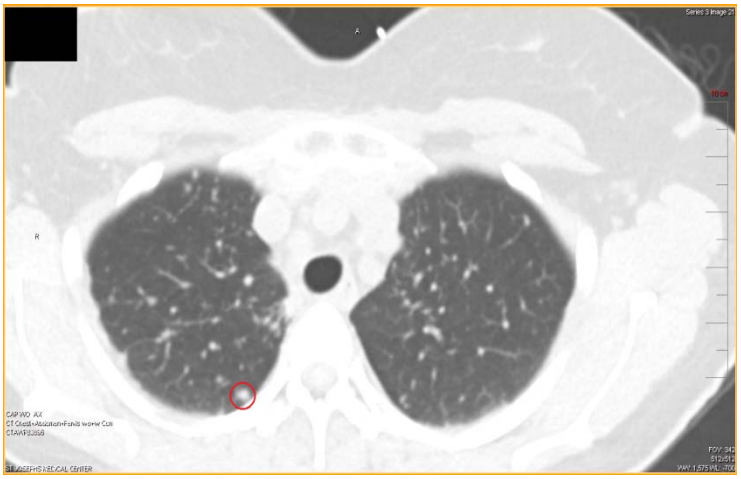

Figure 2. Non-contrast CT showing bilateral pulmonary nodules in the upper lobes, largest of which marked by the red circle

During her hospital stay she was treated with IV fluids, IV Lasix, and a single dose of pamidronate, which resulted in improvement of her serum calcium and renal function. At discharge, her calcium was 8.9 mg/dL, down from 14.4 mg/dL at presentation. Her creatinine was 1.60 mg/dL, down from 2.30 mg/dL at presentation. She was advised to make an appointment with a rheumatologist for follow-up regarding her diagnosis of sarcoidosis.

3. Discussion

Sarcoidosis is a systemic disease characterized by the formation of non-caseating granulomas within various organ groups [10]. The underlying etiology is unknown. [10].

The most common organs affected are the lungs and lymph nodes, with lung or lymph node involvement ranging from 30% to as high as 90% of individuals diagnosed with sarcoidosis [10, 11]. Common respiratory symptoms include cough, dyspnea, and chest discomfort [12]. Radiographic pulmonary manifestations include bilateral or less commonly unilateral hilar adenopathy and/or pulmonary reticular opacities, which may be discovered incidentally [13].

The most common extrapulmonary organs affected are the eyes and skin. Skin involvement occurs in 25 to 35% of patients [14]. Lesions are variable, and can include macules, papules, or plaques visible on the trunk or extremities [14]. Specific related lesions include lupus pernio, an indurated violaceous lesion of the face [14] and erythema nodosum, tender erythematous subcutaneous nodules on the anterior surface of the lower extremities [15]. Lofgren's Syndrome is an acute presentation of sarcoidosis marked by erythema nodosum, arthritis, and bilateral hilar lymphadenopathy seen in 9 to 34% of patients [15]. Eye lesions can include uveitis or keratitis [16].

Renal manifestations are variable. Renal involvement ranges from 0.7 to as high as 48% of patients [17,18]. The most common renal lesion is granulomatous interstitial nephritis, occurring in 7 to 23% of patients [19]. Less common renal lesions include non-granulomatous tubulointerstitial nephritis, retroperitoneal sarcoidosis causing obstructive uropathy, and membranous nephropathy [20].

Cardiovascular manifestations are less common. Pulmonary hypertension occurs in 6 to 23% of patients. [21]. Direct cardiac involvement was found at autopsy in 25% of patients in the US [22]. It can manifest as cor pulmonale, pulmonary fibrosis, third-degree heart block, myocarditis, pericarditis, or congestive heart failure [16].

Neurological manifestations are also less common. Neurological involvement was found at autopsy in up to 25% of patients, but neurological clinical manifestations were only present in 10 to 17% of patients [23]. Symptoms can include headache, ataxia, seizures, or cognitive impairment [24].

Hypercalcemia, the primary manifestation seen in our patient, is present in 10-20% of patients with sarcoidosis [25]. The hypercalcemia is caused by overactivation of mononuclear cells within the non-caseating granulomas. These mononuclear cells express 1α-hydroxylase, which results in increased production of 1,25-dihydroxy-Vitamin D. The increased levels of 1,25-dihydroxy-Vit D increases intestinal calcium absorption. Notably, the 1α-hydroxylase does not respond to negative feedback mechanisms [26]. Thus, an elevated 1,25-dihydroxy-Vit D level, such as in our patient, raises the suspicion for sarcoidosis when patients present with hypercalcemia [26]. While our patient was asymptomatic, patients may have typical symptoms of hypercalcemia. These include nephrolithiasis, bone pains, gastrointestinal disturbances, and neuropsychiatric changes [27].

Having sarcoidosis can lead to an abnormal metabolism of calcium [28]. Kidney function can be adversely affected by elevated calcium due to the effects it has on tubular absorption as well as glomerular function. This can cause renal insufficiency from glomerular permeability damage, prerenal involvement and increased renal vascular resistance from excess calcium ions [28].

There is no specific diagnostic criterion for sarcoidosis. However, diagnosis typically involves clinical and radiographic manifestations, histopathological detection of noncaseating granulomas, and exclusion of other diseases that may present similarly [29]. Laboratory testing that may be beneficial for suspected cases includes the angiotensin-converting-enzyme (ACE) level. ACE level is elevated in 75% of patients with sarcoidosis, including our patient, but is not diagnostic due to poor sensitivity and specificity [30]. Treatment for sarcoidosis primarily involves corticosteroids [31].

References

[1] D. Valeyre, A. Prasse, H. Nunes, Y. Uzunhan, P.-Y. Brillet, and J. Muller-Quernheim, "Sarcoidosis," *The Lancet*, vol. 383, no. 9923, pp. 1155-1167, 2014.

[2] B. A. Rybicki, M. Major, J. Popovich Jr., M. J. Maliarik, and M. C. Iannuzzi, "Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization," *American Journal of Epidemiology*, vol. 145, no. 3, pp. 234-241, 1997.

[3] M. F. Holick, "Vitamin D deficiency," *The New England Journal of Medicine*, vol. 357, no. 3, pp. 266-281, 2007.

[4] R. Karnchanasorn, M. Sarikonda, S. Aldasouqi, and V. V. Gossain, "Severe hypercalcemia and acute renal failure: an unusual presentation of sarcoidosis," *Case Reports in Medicine*, vol. 2010, Article ID 423659, 5 pages, 2010.

[5] R. P. Baughman, A. S. Teirstein, M. A. Judson et al., "Clinical characteristics of patients in a case control study of sarcoidosis," *American Journal of Respiratory and Critical Care Medicine*, vol. 164, no. 10, pp. 1885-1889, 2001.

[6] Nunes H, Bouvry D, Soler P, Valeyre D. Sarcoidosis. *Orphanet J. Rare Dis.* 2007; 2: 46.

[7] Bergner R, Hoffmann M, Waldherr R, Uppenkamp M. Frequency of kidney disease in chronic sarcoidosis. *Sarcoidosis Vasc. Diffuse Lung Dis.* 2003; 20: 126-32.

[8] Mahfoudhi M, Mamlouk H, Turki S, Kheder A. Systemic sarcoidosis complicated of acute renal failure: About 12 cases. *Pan. Afr. Med. J.* 2015; 22: 75.

[9] Casella FJ, Allon M. The kidney in sarcoidosis. *J. Am. Soc. Nephrol.* 1993; 3: 1555-62.

[10] Ibrik O., Samon R., Roda, A. et al., Sarcoidosis: diagnóstico a partir del estúdio de insuficiencia renal e hipercalcemia. Nefrologia 2011, 31(3):371-372.

[11] Rizzato G. Extrapulmonary presentation of sarcoidosis. *Curr. Opin. Pulm.* Med. 2001; 7: 295-7.

[12] A. S. Morgenthau and M. C. Iannuzzi, "Recent advances in sarcoidosis," *Chest*, vol. 139, no. 1, pp. 174-182, 2011.

[13] M. A. Judson, B. W. Thompson, D. L. Rabin et al., "The diagnostic pathway to sarcoidosis," *Chest*, vol. 123, no. 2, pp. 406-412, 2003.

[14] H. Yanardag, "O. N. Pamuk, and G. E. Pamuk, "Lupus pernio" in sarcoidosis: clinical features and treatment outcomes of 14 patients," *Journal of Clinical Rheumatology*, vol. 9, no. 2, pp. 72-76, 2003.

[15] L. E. Siltzbach, D. G. James, E. Neville et al., "Course and prognosis of sarcoidosis around the world," *The American Journal of Medicine*, vol. 57, no. 6, pp. 847-852, 1974

[16] Judson M: Extrapulmonary sarcoidosis. *Semin Respir Crit Care Med* 2007, 28: 83-101.

[17] Nunes H, Bouvry D, Soler P, Valeyre D. Sarcoidosis. *Orphanet J. Rare Dis.* 2007; 2: 46.

[18] Bergner R, Hoffmann M, Waldherr R, Uppenkamp M. Frequency of kidney disease in chronic sarcoidosis. Sarcoidosis *Vasc. Diffuse Lung Dis*. 2003; 20: 126-32.

[19] Berliner AR, Haas M, Choi MJ. Sarcoidosis: The nephrologist's perspective. *Am. J. Kidney Dis*. 2006; 48: 856-70.

[20] Casella FJ, Allon M. The kidney in sarcoidosis. *J. Am. Soc. Nephrol.* 1993; 3: 1555-62.

[21] K. A. Fisher, D. M. Serlin, K. C. Wilson, R. E. Walter, J. S. Berman, and H. W. Farber, "Sarcoidosis-associated pulmonary hypertension: outcome with long-term epoprostenol treatment," *Chest*, vol. 130, no. 5, pp. 1481-1488, 2006.

[22] S. Kim, M. A. Judson, R. Donnino et al., "Cardi sarcoidosis," *American Heart Journal*, vol. 157, no. 1, pp. 9-21, 2009.

[23] C. Kellinghaus, M. Schilling, and P. Ludemann, "Neurosarcoidosis: clinical experience and diagnostic pitfalls, *European Neurology*, vol. 51, no. 2, pp. 84-88, 2004.

[24] E. E. Lower and K. L. Weiss, "Neurosarcoidosis," Clinics in Chest Medicine, vol. 29, no. 3, pp. 475-492, 2008.

[25] O. P. Sharma, "Vitamin D, calcium, and sarcoidosis," *Chest*, vol. 109, no. 2, pp. 535-539, 1996.

[26] Adams JS, Singer FR, Gacad MA et al. Isolation and structural identification of 1,25-dihydroxyvitamin D3 produced by cultured alveolar macrophages in sarcoidosis. *J. Clin. Endocrinol*. Metab. 1985; 60: 960-6.

[27] Inzucchi SE. Understanding hypercalcemia. Its metabolic basis, signs, and symptoms. *Postgrad Med*. 2004 Apr; 115(4): 69-70, 73-6.

[28] Moysés-Neto M, Guimarães FM, Ayoub FH, Vieira-Neto OM, Costa JA, Dantas M. Acute renal failure and hypercalcemia. *Ren Fail*. 2006; 28(2): 153-9.

[29] Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med*. 1999; 160(2): 736.

[30] Studdy PR, Bird R. Serum angiotensin converting enzyme in sarcoidosis--its value in present clinical practice. *Ann Clin Biochem*. 1989; 26 (Pt 1): 13.

[31] Rajakariar R, Sharples EJ, Raftery MJ, Sheaff M, Yaqoob MM: Sarcoid tubulointerstitial nephritis: long-term outcome and response to corticosteroid therapy. *Kidney Int* 2006, 70: 165-169.