

## Unexpected hypercalcemia in a diabetic patient with kidney disease

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### Abstract

We report a case of a diabetic patient with progressive chronic kidney disease and unexplained hypercalcemia. This unusual presentation and the investigation of all possible causes led us to perform a renal biopsy. The systemic sarcoidosis diagnosis was confirmed by the presence of interstitial multiple granulomas composed of epithelioid and multinucleated giant cells delimited by a thin fibrous reaction, and by pulmonary computed tomography finding of numerous lumps with ground-glass appearance. Sarcoidosis most commonly involves lungs, lymph nodes, skin and eyes, whilst kidney is less frequently involved. When it affects males it is characterized by hypercalcemia, hypercalciuria, and progressive loss of renal function. Early treatment with steroids allows for a gradual improvement in renal function and normalization of calcium serum values. Otherwise, the patient would quickly progress to end stage renal disease. Finding of hypercalcemia in a patient with renal failure must alert physicians because it may be a sign of several pathological entities.

**Key words:** Biopsy; Granulomatous; Hypercalcemia; Kidney; Sarcoidosis

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**Core tip:** This report not only describes a case of kidney sarcoidosis, but also explains the diagnostic algorithm that led to the correct diagnosis of a case wrongly labelled

as chronic kidney disease (CKD) secondary to diabetic nephropathy. The absence of other microangiopathic alterations such as retinopathy and secondly the presence of hypercalcemia with hypoparathyroidism in a patient with CKD need to be further explored.

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## INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease with unknown etiology. The diagnosis requires histological confirmation by the discovery of noncaseating granulomas, the exclusion of other diseases with similar symptoms and the clinical evidence of multiple organ involvement<sup>[1]</sup>. It is often subclinical or self-limited or the symptoms are shaded<sup>[2]</sup>. The presentation can be various: respiratory symptoms are not specific and may be mistakenly attributed to other lung diseases, for which empiric therapy may be attempted before other diagnostic tests are performed. Moreover we can find dermatological or ocular abnormalities and totally nonspecific systemic symptoms (fever, weight loss, night sweats). It usually has a benign course with spontaneous resolution in up to two-thirds of cases. However, in one third of cases it is a progressive disorder with significant organ impairment<sup>[3]</sup>.

## CASE REPORT

In October 2013, a caucasian 59-year-old man was admitted to Nephrology division. The history was notable for non-insulin diabetes mellitus (ten years), with poor glycemic control (glycosylated haemoglobin A1c = 10.1%). Two months before he had been hospitalized at the internal medicine ward and insulin therapy had been started. Because of increased creatinine levels with lower limb oedema, the patient was referred to the Nephrology Unit. On admission, physical examination revealed normal blood pressure (120/70 mmHg) and heart rate (100 beats/min), moderate leg oedema; laboratory data showed serum creatinine equal to 2.9 mg/dL, calcium 10.4 mg/dL, proteinuria 156 mg/24 h, calculated creatinine clearance (cCrCl) 30.69 mL/min per 1.73 m<sup>2</sup> (other blood tests are shown in Table 1); electrocardiogram and echocardiogram were normal. Renal ultrasound (Figure 1) and Colour Doppler showed normal kidneys [antero-posterior diameter of right kidney = 11.17 cm, left kidney = 11.48 cm; normal cortico-medullary representation; resistance index (RI) = 0.70 to right, 0.73 to left]. Fundus oculi was negative for typical lesions of diabetic retinopathy. The patient was discharged with diagnosis of "stage III

chronic kidney disease (CKD)" and insulin and antibiotic therapy was recommended. After approximately 1 mo, the patient was hospitalized again due to the worsening of his general conditions and hypercalcemia. He complained of loss of appetite and weakness, with decrease in body weight of about 2 kg. General physical examination was normal except for the presence of right eye hyperaemia, more represented peripheral oedema and reduced breath sounds over the entire pulmonary area. The laboratory tests on the admission are shown in Table 1.

The patient was studied for other secondary causes of hypercalcemia by using an appropriate algorithm<sup>[4]</sup>. Because of the non-PTH mediated further increase in serum calcium (PTH = 5.5 pg/mL), normal level of 25D (21.73 ng/mL) and absence of vitamin D therapy, hematologic screening was performed to exclude cancer. Chest X-ray (Figure 2) detected a parenchymal consolidation in the right hilum, two pseudo nodular thickenings in the base with a diffuse micronodular pattern. Pulmonary computed tomography (CT) (Figure 3) showed multiple ground-glass like lumps involving both lungs, but not in the basal regions, associated with a thickening of the central and peripheral interstitium and multiple reactive mediastinal lymph nodes. Finally, since data were not suggestive for diabetic nephropathy we decided to perform a renal biopsy. Formalin-fixed and paraffin embedded tissue was processed using standard techniques. Light microscopy showed the presence of interstitial multiple granulomas composed of epithelioid and multinucleated giant cells delimited by a thin fibrous reaction (Figures 4 and 5). Edema was present in the interstitium with mild to moderate lymphocyte-monocyte infiltration and tubular atrophy affecting about 15%-20% of the core. Some tubules showed detachment of necrotic cells in the tubular lumen and in some cases rupture of the basement membrane. Arteriolar hyalinosis and arterial intimal fibrosis were also present. Immunofluorescence staining of frozen sections was negative for IgG, IgM, IgA, C3, C1q, fibrinogen, kappa, and lambda light chains.

### Diagnosis

Interstitial Granulomatous nephritis secondary to Sarcoidosis. Arteriosclerosis and arteriolosclerosis.

### Clinical follow up

The patient was treated with oral steroids at the dose of 1 mg/kg per day that was progressively tapered.

Normalization in calcium values and improvement of renal function were observed after the first month of corticosteroid therapy (Table 1). There was also resolution of peripheral oedema and asthenia, and improvement of appetite with progressive body weight increase. At the same time, chest CT showed amelioration of pulmonary alterations and disappearance of lumps.

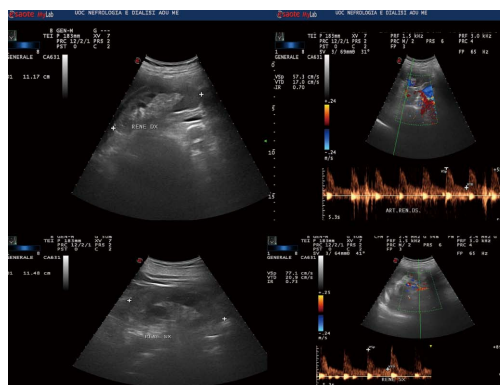
## DISCUSSION

Sarcoidosis most commonly involves lungs, lymph

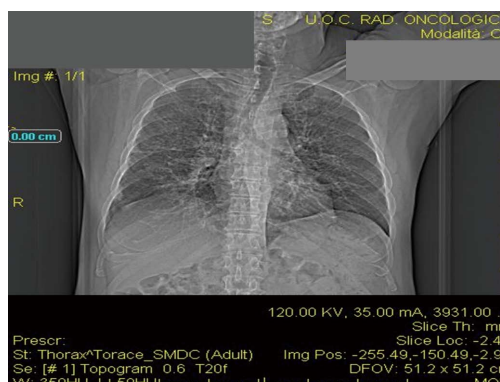
**Table 1** October 2013: laboratory data on first hospitalization; December 2013: laboratory data on second hospitalization before kidney biopsy; January 2014: laboratory data after 1 mo of treatment; February 2014: laboratory data after 2 mo of treatment

Serum chemistries	October 2013	December 2013	January 2014	February 2014
Sodium (mmol/L)	141	136	139	140
Potassium (mmol/L)	38	4.4	4	4.6
Glucose (mg/dL)	139	140	117	145
HbA1c (%)	10.1	9	6.30	7
Proteinuria (mg/24 h)	156	408	328	394
Creatinine (mg/dL)	2.9	3.6	1.83	1.82
eGFR (mL/min per 1.73 m <sup>2</sup> )	30.69	20.69	42	64
Calcium (mg/dL)	10.05	13.01	8.3	8.1
Phosphorus (mg/dL)	4.6	4.2	3.9	4
PTH (pg/mL)	3.50	5.50	59.76	61.38
VIT D3 (ng/mL)	30.67	21.73	20.50	19.83
AST (U/L)	12	15	17	12
ALT (U/L)	9	8	24	9
ALP (U/L)	89	80	79	86
Hematologic studies				
WBC count (x 10 <sup>3</sup> /μL)	10.4	13.6	11.2	10.90
Hemoglobin (g/dL)	10	10.6	13.60	12.2
Platelet count (x 10 <sup>3</sup> /μL)	448	456	432	

nodes, skin and eyes, whilst kidney is less usually affected<sup>[5]</sup>. The disease typically occurs in young and middle-aged black race women. Clinical presentation is different depending on the race. Pulmonary involvement covers 90% of patients, of which 61%-63% are women<sup>[6]</sup>. Among black subjects besides lungs, eyes and skin are often affected. Curiously, calcium metabolism abnormalities are more frequent and more severe in caucasian men with renal interstitial granulomatosis<sup>[6]</sup>. The incidence of renal involvement remains unclear: in autopsy studies, granulomatous infiltrate is found in up to 23% of kidneys, and even up to 48% in small series of biopsies<sup>[7]</sup>. In our case, the characteristic lesions were related to the presence of multiple granulomas consisting of epithelioid and multinucleated giant cells, delimited by a thin fibrous reaction, interstitial oedema with a mild to moderate lymphocyte and monocyte infiltration and tubular atrophy, involving about 15%-20% of the renal tissue. Our patient was initially classified as a case of CKD secondary to diabetic nephropathy in a context of poor glycemic control. However, first of all the absence of other microangiopathic alterations such as diabetic retinopathy and secondly the presence of hypercalcemia with hypoparathyroidism in a patient with CKD needed to be further explored<sup>[8]</sup>. On the second admission, the persistence of hypercalcemia despite the suspension of vitamin D therapy, weight loss, anorexia and asthenia suggested a tubular damage. Differential diagnosis for hypercalcemia at that time was between malignant disease and systemic sarcoidosis. In particular, hypercalcemia characterizes paraneoplastic syndromes<sup>[9-12]</sup> secondary to bronchial carcinoma, small cell lung cancer, breast, gastric and uterus cancer, myeloma, lymphoma. It could be the first clinical manifestation of a parathyroid adenoma; in



**Figure 1** Renal ultrasound.



**Figure 2** Chest X-ray.

an autonomous and independent way, neoplastic tissue produces parathyroid-related hormone (PTHrP), which stimulates bone turnover and calcium reabsorption in the kidney, thus increasing serum calcium values<sup>[13]</sup>. However, in these situations not only calcium but also PTH is elevated, while in our patient PTH was suppressed. We then considered other causes of hypercalcemia, especially an inappropriate intake or increased activation of vitamin D. In the first hypothesis, suspension of oral vitamin D should have led to a normalization of calcium values, but it was not our case. Moreover, the subject was also suffering from CKD, a condition characterized by reduced production of 1- $\alpha$ -hydroxylase and consequently low concentrations of 1,25 dihydroxycholecalciferol<sup>[8]</sup> due to progressive replacement of renal parenchyma with fibrotic tissue. We therefore concluded that hypercalcemia was sustained by an abnormal production of 1- $\alpha$ -hydroxylase from granulocyte monocyte-macrophage cells, secondary to a chronic granulomatous disease without any feed-back mechanism of control: this may lead to calcium retention, hypercalciuria and nephrocalcinosis<sup>[14]</sup>. These situations may be consistent with a diagnosis of sarcoidosis.

Our patient was wrongly categorized as chronic renal failure secondary to diabetes mellitus, whilst it was a case of acute renal injury secondary to sarcoidosis, the identification and treatment of which led to the improvement of renal function. The



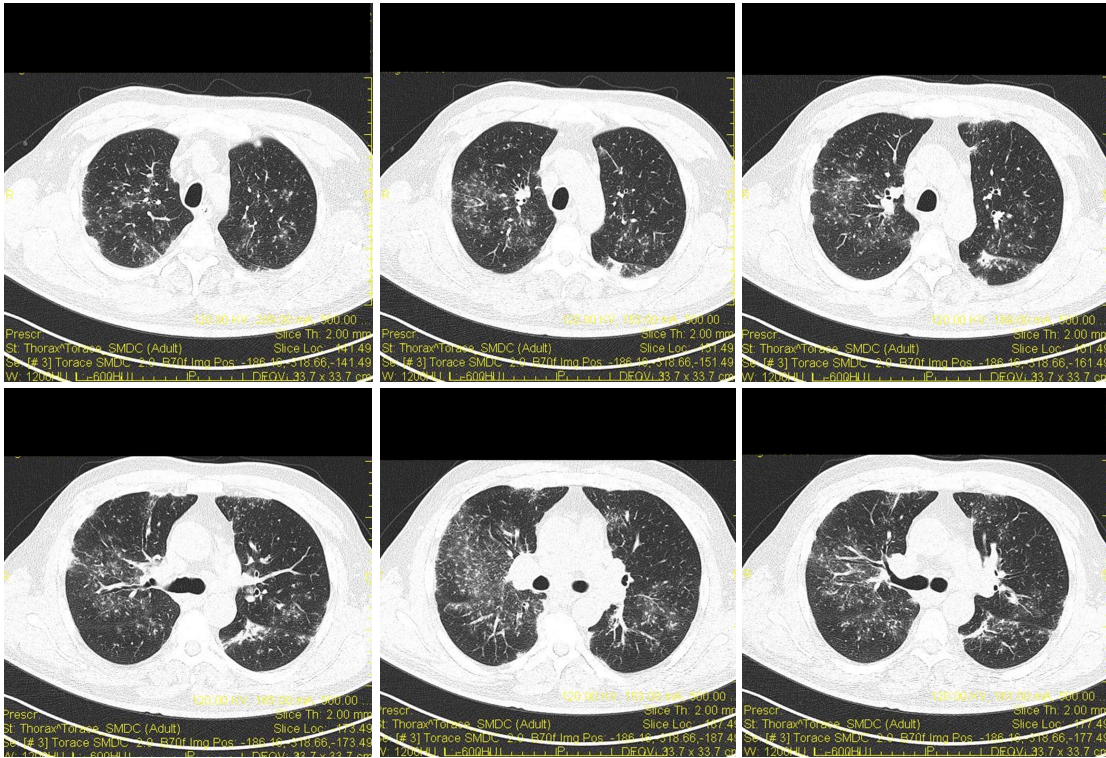


Figure 3 Pulmonary computed tomography.

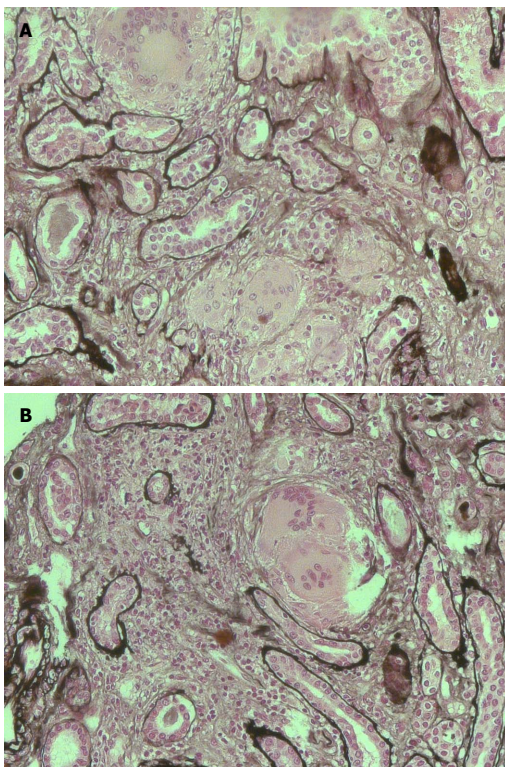


Figure 4 Histological findings. A: Presence of interstitial multiple granulomas composed of epithelioid cells and moderate lymphocyte and monocyte infiltration (silver stain); B: Multinucleated giant cells (silver stain).

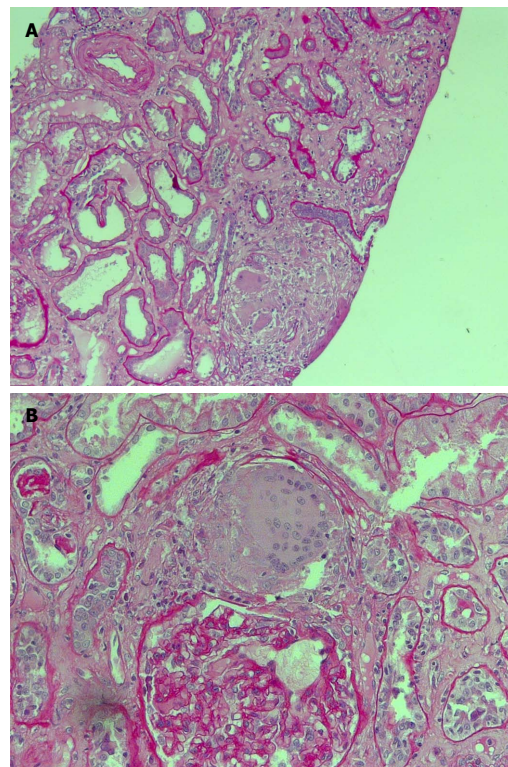


Figure 5 Histological findings. A: Moderate lymphocyte and monocyte infiltration; B: Multinucleated giant cells [periodic acid schiff (PAS) stain].

investigation of all possible causes of “hypercalcemia” allowed to diagnose systemic sarcoidosis confirmed by the evidence of granulomas in renal biopsy. A

comprehensive evaluation should be performed in all patients with suspected sarcoidosis, including history, physical examination, chest radiography, pulmonary

function tests, peripheral blood counts, complete serum chemistries. Pulmonary evaluation starts with function tests (such as spirometry, diffusing capacity, etc.) reveal a restrictive defect with reduced gas exchange and reduced functional status; chest X-ray. Bilateral hilar lymphadenopathy is the most typical sign at chest radiography. Computed tomography (CT) is essentially face for atypical manifestations of the disease, in order to avoid confusion with differential diagnoses and, sometimes, comorbidities. CT typically shows diffuse pulmonary perilymphatic micronodules, with a peribular and fissural distribution and upper and posterior predominance, even when an atypical CT pattern is predominant. CT allows deciphering pulmonary lesions in cases of pulmonary fibrosis, pulmonary hypertension, and airflow limitation<sup>[15]</sup>. Gallium-67-citrate scintigraphy is another imaging method that can be employed both in diagnosis, staging and in the follow-up. Use of fluorine-18-fluorodeoxyglucose positron emission/computed tomography (18F-FDG-PET/CT) seems to have higher diagnostic accuracy with respect to Gallium-67-citrate but the high fee of the method limits its employ. Diagnosis relies on compatible clinical and radiological presentation, evidence of noncaseating granulomas and exclusion of other diseases with a similar presentation or histology. However, there are important variations in diagnostic work-up due to diverse expressions of sarcoidosis and differences in clinical practices among physicians. In our case for example, Gallium-67-citrate scintigraphy, 18F-FDG-PET/CT and serum angiotensin-converting enzyme (ACE) dosage were not made as the result of histological examinations performed on renal tissue was diagnostics. On the other hand, rapid worsening of renal function has been made it necessary to perform biopsy.

In conclusion, we can assume that clinical, laboratory and instrumental data should not be ignored because they are all pieces of a greater puzzle that once rebuilt allows to reach the correct diagnosis and give the right treatment. Like in our case, in a diabetic patient, the presence of hypercalcemia with CKD and the absence of other microangiopathic alterations needs to be further explored because the diagnosis of cancer, paraneoplastic syndrome or parathyroid adenoma has to be excluded as the cause of hypercalcemia.

## COMMENTS

### Case characteristics

A caucasian 59-year-old man with non-insulin diabetes mellitus and poor glycemic control, increased serum creatinine level and hypercalcemia.

### Clinical diagnosis

The patient was initially classified as a case of chronic kidney disease (CKD) secondary to diabetic nephropathy; however, the absence of other microangiopathic alterations in a diabetic patient with CKD needed to be further explored.

### Differential diagnosis

Differential diagnosis for hypercalcemia was with cancer, paraneoplastic syndromes and parathyroid adenoma.

### Laboratory diagnosis

Laboratory data showed serum creatinine 2.9 mg/dL, calcium 10.4 mg/dL,

proteinuria 156 mg/24 h, cCrCl 30.69 mL/min per 1.73 m<sup>2</sup>, PTH 5.5 pg/mL, 25D 21.73 ng/mL.

### Imaging diagnosis

Ultrasound showed normal kidneys. Pulmonary computed tomography revealed multiple ground-glass like lumps involving both lungs.

### Pathological diagnosis

Histological examination showed the presence of interstitial multiple granulomas composed of epithelioid and multinucleated giant cells delimited by a thin fibrous reaction. Oedema was present in the interstitium with mild to moderate lymphocyte and monocyte infiltration and tubular atrophy affecting about 15%-20% of the core.

### Treatment

The patient was treated with oral steroids at the dose of 1 mg/kg per day that was progressively tapered. Normalization in calcium values and improvement of renal function were observed after the first month of corticosteroid therapy.

### Related reports

Sarcoidosis most commonly involves lungs, lymph nodes, skin and eyes, whilst kidney is less frequently affected. The incidence of renal involvement remains unclear: in autopsic studies, granulomatous infiltrate is found in up to 23% of kidneys, and even up to 48% in small series of biopsies.

### Experiences and lessons

The patient was wrongly categorized as chronic renal failure secondary to diabetes mellitus, whilst it was an interesting case of acute kidney injury secondary to sarcoidosis, the identification and treatment of which led to the improvement of renal function.

### Peer-review

It is a good article.

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