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HYPERCALCEMIA AND RENAL AFFECTION: AN UNUSUAL INITIAL PRESENTATION OF SARCOIDOSIS

Pavlina Dzekova-Vidimliski[1], Vesna Ristovska[1], Vlatko Karanfilovski[1], Galina Severova-Andreevska[1], Nikola Gjorgjievski[1], Igor G. Nikolov[1], Biljana Gerasimovska[1], Gordana Petrushevska[2]

[1] University Hospital of Nephrology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, RN Macedonia
[2] Institute of Pathology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, RN Macedonia

Corresponding author: Pavlina Dzekova-Vidimliski, MD, PhD, University Hospital of Nephrology, Blv. Mother Theresa 17, 1000 Skopje, RN Macedonia, Mob tel: ++38975594656, e-mail: pavlinadzekova@yahoo.com

ABSTRACT

Sarcoidosis is a chronic, multisystem, inflammatory granulomatous disease that affects multiple organs in the body, but mostly the lungs and the lymph glands. Hypercalcemia and renal affection are rarely initial presenting features, and in the absence of pulmonary symptoms, the diagnosis of sarcoidosis in those patients could be a diagnostic challenge. A case-patient with sarcoidosis presented with elevated serum calcium and creatinine levels. Renal biopsy showed nephrocalcinosis with chronic fibrosing interstitial nephritis. The extensive mediastinal, abdominal, axillar, and neck lymphadenopathy was presented on the computer tomography scan of the patient's chest and abdomen. The neck lymph node surgical biopsy showed confluent, non-caseating, epithelioid granulomas consistent with sarcoidosis. The serum angiotensin-converting enzyme level was elevated. Treatment with oral prednisolone was started, and improvement of renal function and normalization of serum calcium was noted. Sarcoidosis should be considered in the differential diagnoses in patients with renal impairment and non-parathyroid hormone (non-PTH) dependent hypercalcemia.

Keywords: sarcoidosis, hypercalcemia, granulomas, nephrocalcinosis, renal impairment

INTRODUCTION

Sarcoidosis is an autoimmune, granulomatous disease that predominantly affects the lungs and the lymph nodes (75–90%), followed by other organs such as the eyes, bone marrow, liver, and spleen [1]. Renal involvement is encountered in 5-20% of the patients with sarcoidosis as a part of systemic disease. Only a few articles presented renal involvement as an initial presentation of sarcoidosis [1, 2]. The majority of renal manifestations in sarcoidosis were related to disorders in calcium metabolism. Hypercalciuria was present in up to 62% and hypercalcemia in about 10% of patients with sarcoidosis [1]. Clinically significant sarcoidosis-related hypercalcemia was even rarer and was found in less than 5% of the patients. However, hypercalcemia was more common in patients with renal involvement ranging from 24% to 37% of sarcoidosis patients [3]. Parenchymal renal changes in the form of interstitial nephritis and secondary glomerulopathies were fewer common causes of renal impairment [3].

We present a case patient with sarcoidosis with an initial presentation with hypercalcemia and renal affection.

CASE PRESENTATION

A 39-years-old male was referred to our hospital for evaluation of hypercalcemia with a serum calcium level of 3.3 mmol/l (ref. range: 2.1-2.6 mmol/l) and impaired renal function with a serum creatinine of 175 μmol/l (ref. range: 45-109 μmol/l). The patient complained of weakness, generalized bone pain, low-grade fever, polyuria, and polydipsia for 4-5 months. One year ago, the patient was treated for COVID-19 infection with hepatic lesion and impaired renal function (serum creatinine of 160 μmol/l). The patient denied any chronic diseases and he was not taking any medications regularly. A few mildly enlarged, painless, palpable lymph nodes in the right supraclavicular and axillar region and several erythematosquamous papules on the left upper arm were noted on the physical examination of the patient.

The laboratory analysis showed a high erythrocyte sedimentation rate, elevated total serum protein, elevated serum creatinine, elevated total and ionized serum calcium, and appropriately suppressed parathyroid hormone (PTH) with normal serum vitamin D3 level (Table 1). The serum angiotensin-converting enzyme (ACE) level was elevated at 141.97 U/L (ref. range 0-70 U/L). The serum tumor markers were negative. The 24-hour proteinuria was 0.8 g (<0.2 g), with calcium excretion in 24-hour urine of 9.3 mmol/l (ref. range 1.3-10 mmol/l) (Table 1).

The patient was treated with intravenous fluids, loop diuretics, and bisphosphonates while the etiology of hypercalcemia was being sought. A renal biopsy was done which revealed chronic tubule-interstitial nephritis with nephrocalcinosis, mild to moderate lymphocytic infiltration with tubular atrophy, and interstitial fibrosis (Figure 1).

Further hematologic evaluation and bone marrow biopsy excluded multiple myeloma and other plasma cell dyscrasias. The echocardiography was normal. The chest X-ray showed mediastinal lymphadenopathy. The Computer Tomography (CT) of the chest and the abdomen

Table 1. *Laboratory analysis of the patient on the hospital admission*

Parameters	On admission	Referent values	Parameters	On admission	Referent values
White blood cells ($x10^9$/L)	6.2	4.0-9.0	Phosphorus (mmol/l)	1.0	0.8-1.4
Hemoglobin (g/L)	124	120-180	Alkaline phosphatase (U/L)	92	36-126
Platelet count ($x10^9$/L)	280	150-450	Parathyroid hormone (ng/ml)	12.34	10-69
Albumin (g/L)	42	35-50	Vitamin D3 (ng/ml)	12.9	10-75
Total proteins (g/L)	93	63-83	ACE** (U/L)	141.97	0-70
Erythrocyte sedimentation rate	97	4-15	24 urinary calcium excretion (mmol/l)	9.1	1.3-10
Serum creatinine (μmol/l)	175	45-109	CEA*** (ng/ml)	1.59	< 3.4
Blood urea nitrogen (mmol/l)	7.6	2.7-7.8	AFP† (ng/ml)	2.37	< 9.3
Cacium (mmol/l)	3.2	2.1-2.6	NSE‡ (ng/ml)	11.63	< 16.3
Ionizied calcium (mmol/l)	1.67	1.1-1.3	CYFRA§ 21-1 (μg/L)	3.06	< 3.3
ASO* (U/ml)	794	< 200	PSA‖ (ng/ml)	0.406	0-4

*ASO-antistreptolysin O, **ACE-angiotensin-converting enzyme, ***CEA-carcinoembryonic antigen, †AFP- alpha-fetoprotein, ‡NSE-neuron-specific enolase, §CYFRA- cytokeratin-19 fragment, ‖PSA- prostate specific antigen

showed extensive mediastinal, abdominal, axillar, and neck lymphadenopathy. The fine-needle aspiration biopsy of the neck lymph node and subsequent cytological evaluation revealed the first classification group, highly suspicious for chronic inflammation. The surgical biopsy of the neck lymph showed confluent, non-caseating, epitheloid granulomas consistent with sarcoidosis (Figure 2).

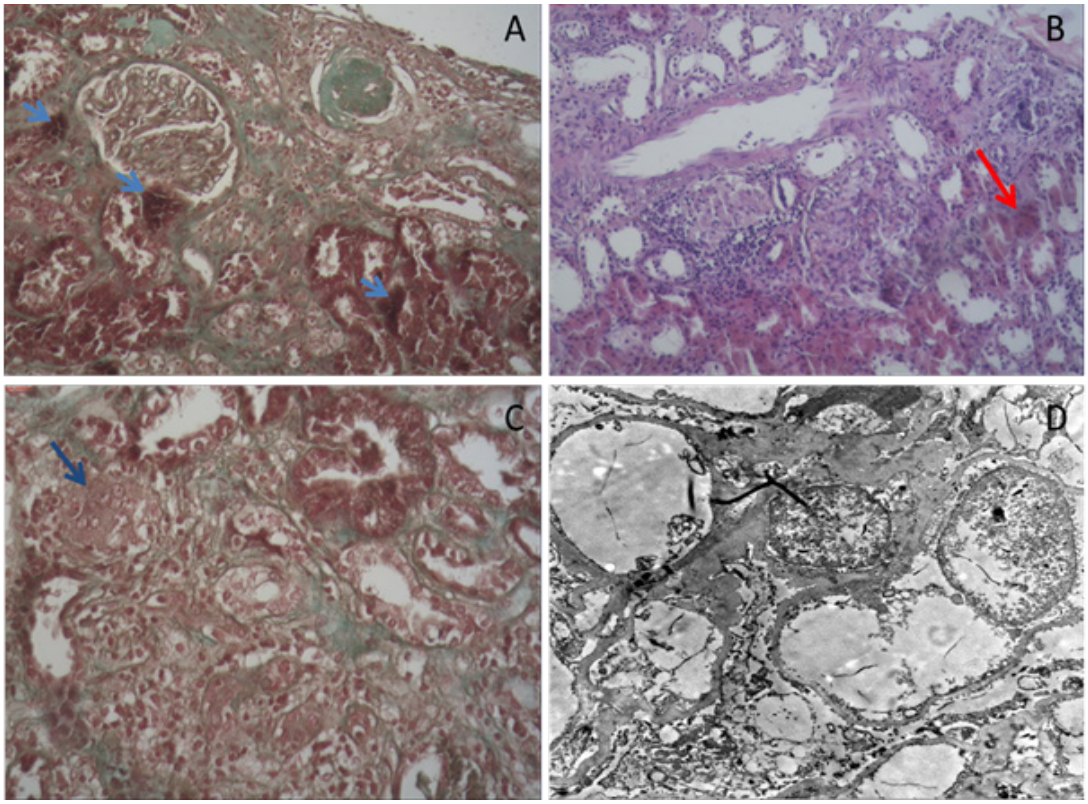

Figure 1. *Renal biopsy showing (A) diffuse interstitial inflammation with fibrosis and calcium deposits (blue arrows; Trichrome staining). (B): multiple small lymphocytes in the renal interstitium and Giant multinucleated cell (red arrow; H&E staining). (C): Giant multinucleated cell (blue arrow; high magnification; Trichrome staining). (D): Electron microscopy of renal interstitium with lymphocytes*

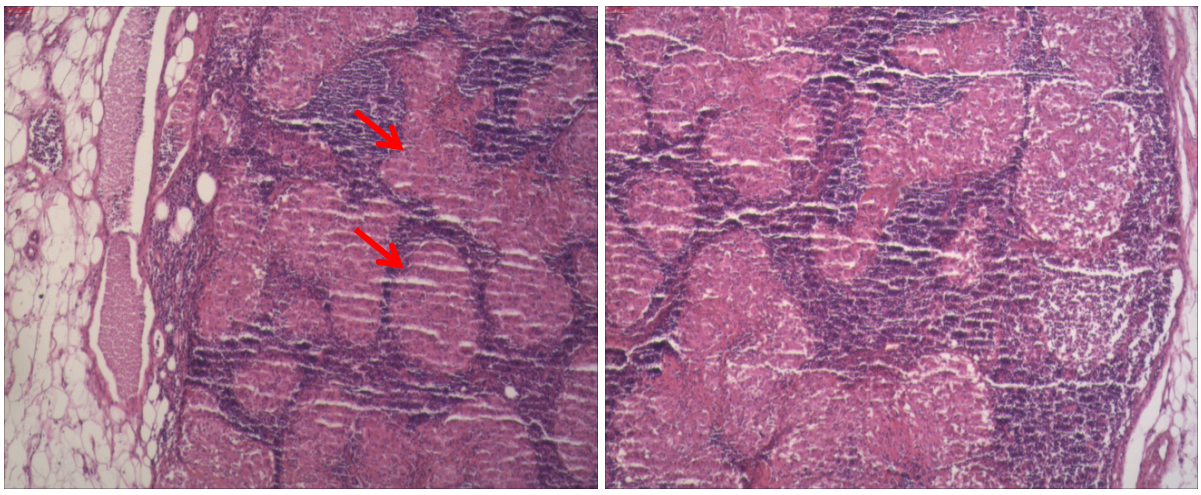

Figure 2. *Lymph node biopsy showing multiple single and confluent non-necrotizing granulomas consistent with sarcoidosis (red arrows; light microscopy, low-power magnification, H&E staining)*

The biopsy of the skin changes confirmed the diagnosis of sarcoidosis. Other systems were studied for the possible involvement of sarcoidosis and revealed no alterations. Treatment with oral corticosteroids (oral prednisolone 0.5 mg/kg/day) was started with complete resolution of hypercalcemia, with improvement in renal function with serum creatinine of 103 μmol/l, and decreased ACE in reference range, two months after initiation of the treatment.

DISCUSSION

Hypercalcemia is a clinical entity encountered in approximately 1% to 2% of the general population and usually is detected on routine laboratory testing. More than 90% of the cases with hypercalcemia were due to primary hyperparathyroidism or malignancy [4]. Hypercalcemia was rarely detected in patients with sarcoidosis. A large single-center retrospective study performed by Baughman et al. (n = 1606 patients), reported that hypercalcemia appeared in about 6% of patients with sarcoidosis. There was no association of hypercalcemia with gender, age, or ethnicity of the patients with sarcoidosis [5]. Hypercalcemia was more frequently noted in patients who presented with sarcoidosis-induced renal injury, indicating that it might play an important role in the pathogenesis of the renal affection [6]. The increased production of 1.25 dihydroxy vitamin D (calcitriol) from activated macrophages in sarcoid granulomas could be the main cause of hypercalcemia in sarcoidosis [5,7]. These macrophages express high levels of enzyme 1-alpha-hydroxylase that leads to increased hydroxylation of preformed 25-dihydroxy vitamin D in the liver, with a rise in serum calcitriol, and increased bowel's calcium absorption [7]. The 1-alpha-hydroxylase from macrophages is less susceptible to feedback inhibition by active vitamin D, which results with high or "inadequate normal" serum vitamin D levels in patients with sarcoidosis [7]. Overproduction of bone-resorbing cytokines and parathyroid hormone-related peptide (PTH rp) might also play a role in the pathogenesis of hypercalcemia in sarcoidosis, especially in patients with normal or low levels of serum calcitriol [8].

Our patient presented with markedly increased serum calcium level and impaired renal function with suppressed PTH levels which suggested that the cause of hypercalcemia was not related to disorders of parathyroid glands. The bone marrow biopsy excluded multiple myeloma as a cause of hypercalcemia and renal affection. The renal biopsy showed chronic interstitial nephritis with nephrocalcinosis, which along with elevated serum levels of ACE, and pathohistological findings from the lymph node and skin biopsy set the final diagnosis of sarcoidosis.

Renal involvement was detected in 0.7%–4.3% of patients with sarcoidosis, and renal failure requiring dialysis treatment in 4%–10% of sarcoidosis patients with renal involvement [9-11]. The renal changes in sarcoidosis could be related to the hypercalcemia and/or additional glomerular, interstitial, and tubular lesions. Hypercalcemia causes vasoconstriction of the afferent renal arteriole with a consecutive decrease in glomerular filtration rate and impaired renal function. It also inhibits sodium-potassium ATPase in renal tubules and tubular action of anti-diuretic hormone (ADH), which leads to polyuria and dehydration [1]. Moreover, chronic hypercalciuria was related to calcification of renal parenchyma (nephrocalcinosis) with chronic interstitial inflammation and ultimately fibrosis with the development of chronic renal disease [1,7]. Nephrolithiasis was found in 10% of patients with sarcoidosis [12]. Aside from hypercalcemia, the other causes for renal impairment in sarcoidosis were: granulomatous tubulointerstitial nephritis (GIN), tubulointerstitial nephritis without granulomas, obstructive uropathy, and a wide range of secondary glomerular diseases (membranous nephropathy, IgA nephropathy, crescentic glomerulonephritis, focal segmental sclerosis and membranoproliferative glomerulonephritis) [13,14]. Granulomatous tubulointerstitial nephritis (GIN) was the most frequent cause of renal impairment in sarcoidosis in 37%–79% of renal biopsy specimens [3]. The presence of hypercalcemia with hypercalciuria and tubulointerstitial nephritis without granulomas were the causes of renal affection in our case patient. Pathohistological evaluation of the renal biopsy specimen showed nephrocalcinosis with chronic fibrosing interstitial nephritis.

The treatment of hypercalcemia associated with sarcoidosis includes rehydration, loop diuretics to promote calcium excretion, bisphosphonates, and corticosteroids [15]. Corticosteroids (prednisone 30 to 60 mg/day) are the first-

line therapy associated with improvement in the clinical manifestations of sarcoidosis and lowered hypercalcemia and hypercalciuria [1].

Hydroxychloroquine and ketoconazole might be used as alternative treatment options. The treatment of renal involvement in sarcoidosis patients usually starts very late in the course of the disease, with chronic changes of renal parenchyma, which imposed the need to use longer than usual corticosteroid treatments, or additional immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate or infliximab [1]. The small minority of patients who present with sarcoidosis-associated acute renal disease had complete treatment response and excellent prognosis [16,17]. There is no standardized protocol regarding the dose and duration of therapy for renal sarcoidosis. Rajakaria R. et al. analyzed 39 patients with sarcoid interstitial nephritis, as in our case, with excellent response to corticosteroid therapy even in patients with advanced chronic changes on renal biopsy. There was a significant improvement in glomerular filtration rate (GFR) from 28 ± 14 ml/min/1.73 m2 at presentation to 49.6 ± 5.2 ml/min/1.73 m2 at 1 year, suggesting that maintenance treatment with low-dose corticosteroids improved renal function, prevented relapses, and progression to renal failure [6]. Another series of patients indicated that prednisolone 0.5 mg/kg with slow tapering of the dose in the next 18-37 months was sufficient to induce remission of sarcoidosis with minimal adverse events compared to a higher dose (1 mg/kg) and longer duration of the treatment [18]. More aggressive treatment approaches were advised for patients with granulomatous tubulointerstitial nephritis and concomitant membranous and focal proliferative GN as well as with lung and heart involvement. However, despite the good treatment response, only one of seven patients was with recovered renal function [6]. The case patient with chronic tubule-interstitial nephritis with nephrocalcinosis was treated with prednisolone (0.5 mg/kg/day), with complete resolution of hypercalcemia, improvement in the renal function, and remission of sarcoidosis, after two months of the treatment start. The remission of the disease and the normal renal function in the case patient was maintained with slow tapering of the prednisolone dose to 0.25 mg/kg/day in the next four months.

CONCLUSION

Sarcoidosis should be considered in the differential diagnoses in patients with renal impairment and non-PTH-dependent hypercalcemia. Early diagnosis and initiation of corticosteroid treatment could prevent further deterioration and even reverse impaired renal function in these patients.

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Резиме

ХИПЕРКАЛЦЕМИЈА И БУБРЕЖНА АФЕКЦИЈА: НЕОБИЧНА ПОЧЕТНА ПРЕЗЕНТАЦИЈА НА САРКОИДОЗА

Павлина Џекова-Видимлиски[1], Весна Ристовска[1], Влатко Каранфиловски[1], Галина Северова-Андреевска[1], Никола Ѓорѓиевски[1], Игор Г. Николов[1], Билјана Герасимовска[1], Гордана Петрушевска[2]

[1] Универзитетска клиника за нефрологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, РС Македонија

[2] Институт за патологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“, Скопје, РС Македонија

Саркоидозата е хронична, мултисистемска, воспалителна, грануломатозна болест, која зафаќа повеќе органи во телото, но најмногу белите дробови и лимфните жлезди. Многу ретко хиперкалцемијата и бубрежната афекција во отсуство на белодробни симптоми можат да бидат единствена клиничка презентација на саркоидозата. Презентираме болен со саркоидоза, кој беше упатен за дијагностички иследувања поради наод на покачено серумско ниво на калциум и на креатинин. Бубрежната биопсија покажа присуство на нефрокалциноза со хроничен фиброзен интерстицијален нефритис. Наодот од компјутерската томографија на градниот кош и абдоменот на болниот беше претставен со екстензивната медијастинална, абдоминална, аксиларна и вратна лимфаденопатија. Со хируршка биопсија на лимфните јазли на вратот на болниот се детектираше присуство на конфлуентни, неказеозни, епителиоидни грануломи конзистентни со саркоидоза. Нивото на ангиотензин конвертирачкиот ензим во серумот на болниот беше покачено. Третманот на болниот со орален преднизолон доведе до постепено подобрување на бубрежната функција и нормализирање на серумскиот калциум. Саркоидозата треба да се земе предвид како диференцијална дијагноза кај болните со бубрежно оштетување и хиперкалцемија што не е предизвикана од хиперпаратироидизам.

Клучни зборови: саркоидоза, хиперкалцемија, грануломи, нефрокалциноза, бубрежно оштетување