Article published online: 2021-08-09

CASE REPORT

Renal confined sarcoidosis: Natural history and diagnostic challenge

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Access this article online

Website: www.avicennajmed.com

DOI: 10.4103/2231-0770.130346

Quick Response Code:

ABSTRACT

A 69 year old male referred to nephrology clinic for uncontrolled hypertension. During his follow up over two years, he developed renal disease and hypercalcemia. He was found to have monoclonal gammopathy (MGUS). Urinalysis was negative except for Monoclonal IgG on immunoelectrophoresis. Workup for malignancy was negative including chest X-ray and bone marrow biopsy. He progressed into renal failure and ended up on dialysis. Interestingly, the renal biopsy showed non-caseating granulomas, and the patient was diagnosed with renal confined sarcoidosis which is extremely rare. PPD was negative. He was treated with Prednisone 60 mg daily. Surprisingly, his kidney disease was not responsive to steroids. Despite improvement in his calcium with treatment, his kidney function did not improve and he remained on hemodialysis but needed to stay on small dose of Prednisone to keep his calcium under control. Our case is the first in the literature that demonstrates the natural history of renal-confined sarcoidosis. In addition, the presence of MGUS created a diagnostic challenge and delayed diagnosis of sarcoidosis. Although the renal biopsy did not show direct damage from MGUS, a potential relation between renal sarcoidosis and MGUS is worth studied.

Key words: Hypercalcemia, monoclonal gammopathy of undetermined significance, renal-confined sarcoidosis

INTRODUCTION

Kidney failure caused by granulomatous interstitial nephritis (GIN) in the absence of extra renal sarcoidosis is an extremely rare clinical condition.[1] Renal sarcoidosis can present with a constellation of clinical symptoms. The most frequently observed pathology was metabolic derangement of calcium.[2] This includes increased serum and urinary levels of calcium and deposition of calcium within the kidney.[2] A renal specific manifestation of sarcoidosis is interstitial nephritis. In a retrospective study of 40 cases, the most common renal manifestation of sarcoidosis was observed to be granulomatous tubulointerstitial nephritis.[3] Renal granulomatoses reported frequency ranged from 0.5% to 0.9% of renal biopsies with most frequent etiologies are sarcoidosis, medications, infections and Wegener granulomatosis, but many other causes have been reported in the literature.[3] Although, it usually manifests as acute or chronic renal insufficiency, renal insufficiency due to interstitial infiltration was observed in <1% of patients with sarcoidosis.[3] In addition, it has been suggested that GIN with no ascertainable etiology may be a feature of renal-confined sarcoidosis.[4] Renal-confined sarcoidosis resistant to medical treatment is an extreme rare phenomenon. In seven GIN cases of renal limited sarcoidosis presented by Robson *et al*., the majority of patient demonstrated improving kidney function while on steroid treatment; however, only to sub-normal values.[4] Only two of these cases were refractory to steroids and advanced to end stage renal disease.[4] It has been suggested that the presence of interstitial fibrosis is an important factor dictating the responsiveness to treatment in renal sarcoidosis; however, this finding was derived from patients who presented initially with non-renal confined sarcoidosis.[5]

CASE REPORT

The present case report is about a 69-year-old male patient who was referred to nephrology for persistent and

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worsening hypertension for 2 years despite taking multiple anti-hypertensive medications. No other complaints. Past medical history included obstructive sleep apnea, diabetes mellitus type 2, atrial fibrillation, hypothyroidism, gastro esophageal reflux disease, renal cysts, fatty liver, gout, dyslipidemia and benign prostatic hyperplasia. Social history and family history were unremarkable.

Patient had negative 24 urinary catecholamines, arterial Doppler studies of the renal arteries and renal computed tomographic angiography. Initial ancillary laboratory findings were unremarkable including renin, aldosterone, parathyroid hormone (PTH) and calcium levels. He had borderline normal renal function (serum creatinine = 1.2, glomerular filtration rate [GFR] >60). Urinalysis was normal. Blood pressure improved to normal on atenolol, nifedipine, lisinopril. Patient also demonstrated low vitamin D 25-hydroxy levels and was consequently started on replacement with ergocalciferol.

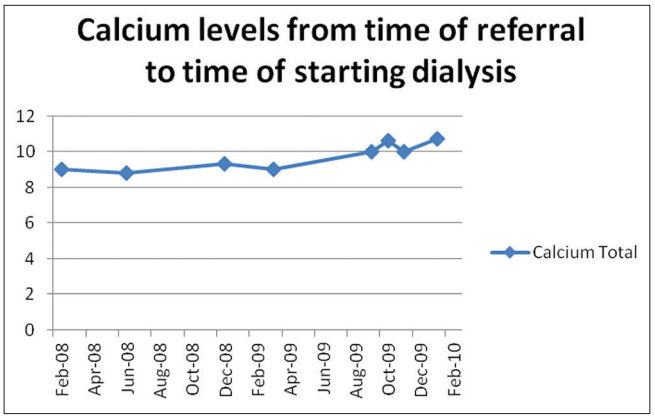
Within 6 months of initial nephrology work-up, the patient continued to demonstrate stable blood pressure, renal function and blood counts.

Unexpectedly, 8 months later, the patient's GFR dropped to 58 and he had slight anemia with hemoglobin level of 12.9. Blood pressure remained stable. His calcium, PTH and vitamin D - 25 levels were all within the normal limits. Around 10 months post referral, serum protein electrophoresis demonstrated an IgG kappa monoclonal spike and GFR decreased to 55 (chronic kidney disease stage 3). His calcium and PTH were normal. Urinalysis was negative except for monoclonal IgG on immunoelectrophoresis, but no light chains detected. At this time, patient was referred to hematology-oncology specialist and a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was established through bone marrow biopsy. Final pathologic diagnosis was: A, B, C. Bone marrow, aspirate/imprint smears, clot and biopsy sections, Hypercellular marrow for age (80% cellularity) with increased myelopoiesis and mild dysmegakaryopoiesis. Absent iron stores, marrow, with decreased sideroblastic iron, compatible with iron deficiency anemia pattern. Less than 10% plasma cells with kappa excess (by CD138 and kappa/lambda immunostaining), most compatible with a MGUS.

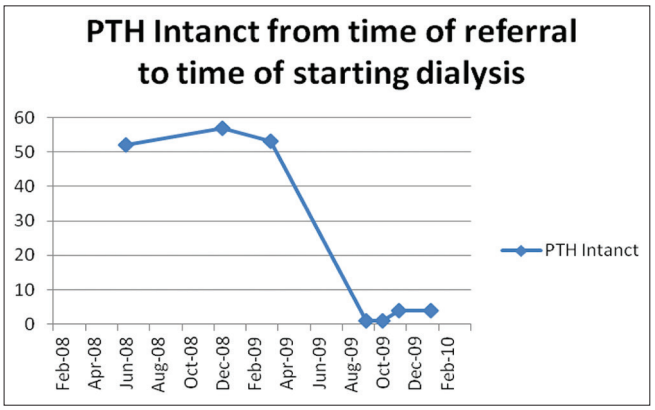
At approximately 16 months later, the patient stated noticing elevated blood pressure reading and started to develop symptoms of malaise and fatigue. Within 2 months (18-20 months post-nephrology referral), the patient's renal function declined abruptly (GFR 32) and was also demonstrating bone mineral disease with worsening hypercalcemia (calcium 10.6 mg/dL) and low PTH (<1 pg/mL) [Graphs 1 and 2].

Given the history of monoclonal gammopathy, the concern and working diagnosis included the possibility of a plasma cell dyscrasia. However, repeat serum protein electrophoreses was not impressive and anemia was only mild (12.6). The oncologist suggested that worsening calcium levels and renal failure could represent milk alkali syndrome, given dietary history where the patient was consuming three glasses of milk per day. Within the next 3 months (21-23 months post nephrology referral), the calcium levels slightly dropped after the cessation of milk intake, but rebounded again with no identifiable cause (calcium 10.7). More importantly, the renal function showed significant aberration and decline within these months (GFR was 8); necessitating dialysis for end-stage renal disease (ESRD) and a drastic revision in diagnostic approach.

Repeated renal ultrasound showed cortical atrophy and no hydronephrosis. Chest radiographic imaging was negative and skeletal survey was showed no lytic or other bone related lesions. Renal biopsy was ordered due to unexplained and unexpected worsening of renal function.



Graph 1: Calcium levels from time of referral to time of starting dialysis



Graph 2: Parathyroid hormone intact from time of referral to time of staring dialysis

Renal pathology

Light microscope

H and E, periodic acid-Schiff, Lillie's allochrome and Jones' silver stained section of the renal cortex and medulla. Evaluation demonstrated diffuse tubular atrophy involving 90% of tubules examined. The luminae contained cellular debris or protein casts with cellular response [Figure 1].

Mononuclear cell infiltrates with non-necrotizing granulomatous inflammation and eosinophils were noted-granulomatous interstitial inflammation with eosinophils [Figure 1].

Immunofluorescence

Direct immunofluorescence with fluorescein isothiocyanate conjugated antisera (IgG, IgA, IgM, C3, C1q, albumin, fibrinogen and kappa and lambda light chains revealed no glomerular or tubulointerstitial staining. This aforementioned finding excludes immune complex glomerulonephritis [Figure 2].

Electron microscopy

Analysis of one glomerulus selected for examination demonstrated no electron dense deposits, no amyloid type fibrils, no tubuloreticular inclusions and normal thickness of glomerular basement membrane.

Acid fast bacilli strain

Negative stain to detect for mycobacteria or other acid fast organisms.

Findings summary

The significant finding obtained from renal biopsy revealed granulomatous interstitial inflammation with eosinophils consistent with renal sarcoidosis. His purified protein derivative skin test was negative.

His angiotensin converting enzyme (ACE) level was high (73 units/L) and PTH level was still low (4 pg/mL) 24 months after the initial referral. Vitamin D1/25 dihydroxy level was checked later and was elevated (148 pg/mL).

In light of ESRD and a conclusive diagnosis of renal-confined sarcoidosis, the patient was begun on prednisone (60 mg daily) and enrolled in a hemodialysis program. Within 1 month, the patient's hypercalcemia resolved and remained within normal values up to 3 years for a majority of the time-course. ACE, PTH and vitamin D1/25 dihydroxy improved as well. Despite the improvement of his calcium, the patient's renal function continued to be refractory to steroid treatment and remained on dialysis for persistent ESRD.

DISCUSSION

Common signs of renal sarcoidosis include hypercalcemia and renal failure secondary to GIN.[2] Since hypercalcemia and renal dysfunction can occur simultaneously in a whole host of pathologies, differentiating between renal diseases in the setting of other underlying co-morbidities can be challenging. In this case, during the pre-dialysis phase described above, the patient presented with worsening renal function, hypercalcemia and mild anemia. He had abnormal monoclonal protein on serum protein electrophoresis (monoclonal IgG spike) and a history of underlying and biopsy proven monoclonal gammopathy. Hence, arriving at a diagnosis suggestive of renal sarcoidosis using clinically, laboratory and radiographic parameters was challenging. In fact, the concern and working diagnosis focused on the possibility of a plasma cell dyscrasia that had transformed. However, since repeat SPE and anemia was unimpressive and the skeletal survey imaging was negative, the oncological impression was that the patient's declining

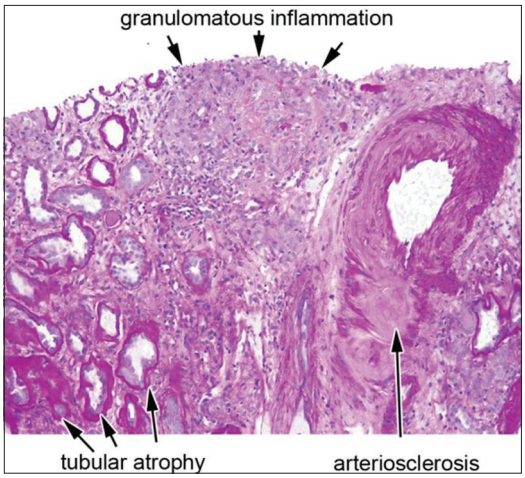


Figure 1: Light microscope

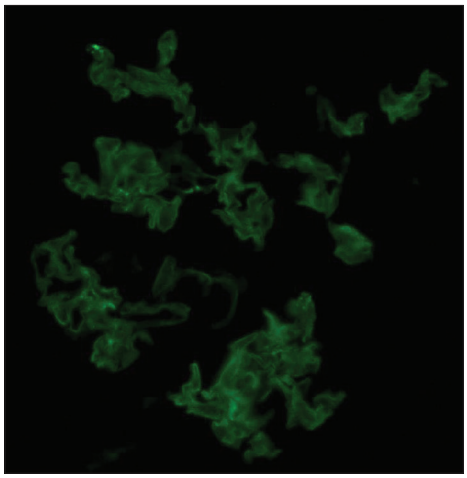


Figure 2: Immunofluorescence

renal function with hypercalcemia was not attributed by a plasma cell dyscrasia.

Hence, in retrospect we suggest that performing both a renal biopsy and hematological work-up in the presence of unexplained worsening renal function, hypercalcemia and underlying monoclonal gammopathy is important toward establishing a definitive diagnosis.

In a review of the literature, only two cases of renal isolated sarcoidosis failed to demonstrate responsiveness to steroid treatment and progressively advanced to ESRD.[4,6,7] Of the patients who presented initially with ESRD, all responded to steroids and were able to depart from dialysis.[4,7] In our case, given the questionable etiology due to an underlying hematologic co-morbidity, the patient progressed to ESRD prior to initiating steroid treatment. However, unlike the other cases mentioned in the literature, our patient was unable to relinquish dialysis.

Furthermore, our patient is the only case with ESRD who demonstrated concomitant hypercalcemia (corrected) prior to initiating treatment. Hence, whether elevated calcium levels is a valuable biochemical marker in predicting responsiveness to steroids in ESRD secondary to renal-confined sarcoidosis, is worth investigating. Although, the renal biopsy did not show direct damage from MGUS, a potential relation between renal sarcoidosis and MGUS that makes it refractory to treatment is worth studied.

All cases of renal isolated sarcoidosis reviewed in the literature describe patients who initially present with impaired renal function.[3,5,6] Interestingly, our patient presents the first case where renal function was normal upon presentation. He lacked any manifesting symptoms or lab abnormalities of renal failure or sarcoidosis upon presentation. Hence, the time-course of our patient as outlined above, may reflect the natural history of renal-confined sarcoidosis. From our experience, the decline from baseline renal function (with normal calcium levels) to ESRD (with hypercalcemia) in the absence of steroid treatment was approximately within 2 years (23 and 24 months).

Since renal sarcoidosis can respond rapidly to steroids, the importance of its consideration with patients with renal failure has been suggested.[5] A progressive decline to ESRD within a 2 year window may occur in patients with renal confined sarcoidosis. Given the aggressive nature of the disease, we suggest that establishing the diagnosis and initiating treatment within this timeframe can prove to be crucial.

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Cite this article as: Ghafoor A, Almakki A. Renal confined sarcoidosis: Natural history and diagnostic challenge. Avicenna J Med 2014;4:44-7.

Source of Support: Nil, **Conflict of Interest:** None declared.