Abstract
We report a case of nephrocalcinosis with renal failure which on evaluation was found to have hypercalcemia. Further investigations showed an inappropriately normal intact parathormone (iPTH) and 1,25 dihydroxy-vitamin D level in the setting of renal failure. Probing for a cause of non-PTH mediated hypercalcemia led to the diagnosis of sarcoidosis. Treatment with glucocorticoids could partially reverse the renal failure and control the hypercalcemia. This case illustrates the importance of careful interpretation of laboratory parameters especially levels of iPTH and Vitamin D metabolites in renal failure.

Introduction
There are several causes of hypercalcemia in patients with chronic renal failure. We report a very rare case of a patient presenting with renal failure and hypercalcemia which was eventually diagnosed to be due to sarcoidosis. This case highlights the importance of considering alternate explanation for hypercalcemia other than hyperparathyroidism in patients with nephrocalcinosis and renal failure. In addition, we also point out the clinical clues which alerted us to the diagnosis of sarcoidosis in this case.

Case Report
A 47 year old male was referred to our tertiary care endocrine center for evaluation of hypercalcemia associated with renal failure. He was apparently well till 5 years ago, when he presented elsewhere with generalized tiredness, anorexia and history of passing stones in the urine. At that time he was diagnosed to have bilateral nephrocalcinosis and renal failure with a serum creatinine of 9 mg/dl for which he underwent lithotripsy following which he improved symptomatically and the serum creatinine came down to 2 mg/dl. no reports of his calcium profile at that time were available. Two years later he had a recurrence of his symptoms and he underwent lithotripsy once more. Now he presented to the referring physician with progressive itching throughout the body and pain both legs with intermittent passage of stones in the urine. He also had history of class 2 exertional dyspnoea and occasional dry cough for the last 2 years. Investigations done at this time revealed a serum creatinine of 2 mg/dl, serum calcium of 12.5 (8.6-10.2) mg/dl, phosphorus of 5.7 (2.5-4.5) mg/dl, and an iPTH of 28 (15-68) pg/ml. A 24 hour urine calcium of 423.4 mg. Serum ACE levels were 164 U/L (9-67). Work up for multiple myeloma and tuberculosis were negative. Skeletal survey and whole body skeletal scintigraphy showed no evidence of any metabolic bone disease. Chest X ray revealed left upper lobe lung fibrosis (Figure 1). Pulmonary function tests showed a restrictive lung disease pattern and non contrast HRCT lungs and abdomen confirmed the presence of fibrosis in left upper lobe of lungs, splenomegaly with coarse parenchymal echotexture and bilateral medullary nephrocalcinosis with small shrunken kidneys (Figure 2).

In the presence of hypercalcemia and hyperphosphatemia with renal failure, and an inappropriately low PTH for the renal failure, a non-PTH mediated cause for the hypercalcemia was thought of. The additional findings of splenomegaly and left upper lobe fibrosis made sarcoidosis the most probable diagnosis.

Fig. 1 : Chest X Ray Showing Left Upper Lobe Fibrosis
Fig. 2: Computed Tomography of the Abdomen Showing Spleenomegaly and Nephrocalcinosis

Fig. 3: Histopathology of Bone marrow showing Non Caseating Granuloma

Serum ACE levels were elevated and 1, 25 di hydroxy-vitamin D was inappropriately normal for the degree of renal failure. A bone marrow biopsy was done which revealed normocellular marrow with trilineage maturation and focal non-caseating granulomas which were AFB (Acid Fast Bacilli) and PAS (Periodic Acid Shiff) negative suggestive of sarcoidosis (Figure 3).

To summarise, this gentleman had non-PTH mediated hypercalcemia with hyperphosphatemia with renal failure along with spleenomegaly, medullary nephrocalcinosis, an elevated ACE level and inappropriately normal 1, 25 dihydroxy-vitamin D levels with non-caseating granuloma in the bone marrow. So a diagnosis of sarcoidosis was made and a decision was taken to see the therapeutic response to glucocorticoids. Further confirmatory tests including a transbronchial lung biopsy and a renal biopsy were planned if there was no response to steroids.

Patient was started on 0.5 mg /kg of oral prednisolone and gradually tapered over the next 6 months to 5 mg prednisolone daily. The serum calcium improved within a week of starting steroids and the renal failure too improved which has ever since remained stable at a serum creatinine of 4 mg/dl. Initially there was slight worsening of the hypercalcuria which later settled. At the time of last follow up, patient has a normal serum calcium level and a stable renal function with relief of his itching.

Discussion

Sarcoidosis presenting as renal failure with nephrocalcinosis and hypercalcemia is rare. The immediate differential diagnosis of hypercalcemia with nephrocalcinosis and renal failure is hyperparathyroidism either primary or tertiary. The PTH levels usually are elevated due to secondary hyperparathyroidism in renal failure. An inappropriately normal PTH in renal failure should point towards a non PTH mediated cause for the hypercalcemia which can be either PTHrP mediated or vitamin D mediated. The cause for hypercalcemia in sarcoidosis is the expression of 1 alpha hydroxylase by the macrophages in the granulomas which convert 25 hydroxy-vitamin D into 1, 25 dihydroxy-vitamin D which is the active metabolite which helps in the absorption of calcium and phosphorous from the intestine and also renal reabsorption of calcium and phosphorous. The proximal tubules are the main site of production of 1, 25 dihydroxy-Vitamin D normally and in renal failure their levels will be very low. Our patient had an inappropriately normal 1, 25 di-OH-Vitamin D for the degree of renal failure which indicates an extrarenal source of 1 alpha hydroxylase. The presence of hypercalcemia associated with renal failure is a good prognostic indicator in sarcoidosis; patients with hypercalcemia will improve their renal failure more often with steroids than those without hypercalcemia. Raised serum ACE levels are very nonspecific and can be seen in a variety of conditions apart from sarcoidosis. The causes of renal failure in sarcoidosis are interstitial nephritis, nephrocalcinosis and sarcoid glomerulopathy. Our patient definitely had nephrocalcinosis and in the absence of renal biopsy, the presence of other components cannot be confirmed. Spleenomegaly in sarcoidosis is also variable and has been reported in 2-40 % of cases. The presence of spleenomegaly portends more extrathoracic involvement and splenectomy is indicated only in severe hypersplenism, prophylaxis of splenic rupture and neoplastic exclusion. A single case report of coexisting primary hyperparathyroidism with sarcoidosis who presented with severe hypercalcemia and renal failure has been published in Endocrine Journal in 2008.

To conclude, this case highlights the importance of considering the diagnosis of rare diseases like sarcoidosis induced hypercalcemia in patients presenting with nephrocalcinosis and renal failure, the treatment of which can potentially prevent progression to end stage renal failure. The importance of interpreting serum levels of iPTH and vitamin D metabolites in renal failure is also highlighted.

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