Hypercalcemia Secondary to Sarcoidosis Associated with Membranous Nephropathy

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Received Date: 01 November, 2019; Accepted Date: 11 November, 2019; Published Date: 15 November, 2019

Abstract

We present a man referred for etiological study of hypercalcemia and renal impairment who previously developed a nephrotic syndrome two years ago with negative antiPLA2R antibodies in serum determination and negative PLA2R expression in glomeruli. He presented a constitutional syndrome and systemic lymphadenopathy suggesting a lymphoproliferative process with secondary hypercalcemia. Adenopathy biopsy showed granulomas and Langhans cells as histological data of sarcoidosis. Partial improvement of renal function and hypercalcemia were reached with corticotherapy in follow up. An increase in calcium reabsorption, bone metabolism or decreased excretion is necessary to justify hypercalcemia. Therefore, sarcoidosis should be considered in patients with MN and hypercalcemia.

Keywords: Acute Renal Failure; Corticotherapy; Glomerulonephritis; Hypercalcemia; Membranous Nephropathy; Sarcoidosis; Systemic Diseases

Case Report

A 32-year-old man referred for etiological study of hypercalcemia and renal impairment. He developed a nephrotic syndrome in 2016 with histological diagnosis compatible with Membranous Nephropathy (MN) with negative antiPLA2R in serum and negative PLA2 receptor expression in glomeruli on renal biopsy (Figure 1). When he was admitted blood tests showed hypercalcemia 12.8 mg/dl associated with deterioration of renal function with serum creatinine of 2.13 mg/dl (baseline 1.1 mg/dl), proteinuria 2.2 g/day, albuminuria 1.3g/day, calcium in urine 274mg/24h, phosphate 2.3 mg/dl, PTH 12 ng/L, 25OHVitamin-D 17ug/L. He showed signs of water depletion and a constitutional syndrome with loss of 10 kg in the last year, intermittent fever and submandibular, cervical and supraclavicular lymphadenopathy on physical examination.

He was on antihypertensive treatment with angiotensin converting enzyme inhibitors and thiazides. For all the clinical data, an extension study was performed to rule out malignancy. Thoracoabdominopelvic CT study (Figure 2) showed multiple supra and infradiaphragmatic adenopathies and associated splenomegaly suggestive of lymphoproliferative process. Multiple myeloma and infectious diseases screening were performed, being all results negatives. A lymphoproliferative process was suspected as the most likely cause of hypercalcemia and constitutional syndrome. Clavicular adenopathy biopsy and bone marrow biopsy were performed(Figure 1). Bone marrow biopsy was normocellular. Adenopathy biopsy showed the presence of granulomas with epithelioid cells and dispersed Langhans cells with Schaumann bodies without necrosis or visualization of microorganisms, compatible with histological data of Sarcoidosis.
Figure 1: (A) Lymph node. 1.6x. H&E, (B) Lymph node with Langhans cells and epithelial cells within granulomas 10x. H&E. Kidney, (C) Thickening of GBM. 20x H&E, (D) Contours irregularities and spikes. Silver-methenamine 63x, (E) granular deposits IgG Direct Immunofluorescence 20x, (F) IgG4 20x immunohistochemistry peroxidase, and (G) Anti-PLA2R 20x immunohistochemistry peroxidase.

Figure 2: Axial cuts on CT showing submandibular and mediastinal adenopathy. 78x44mm (300 x 300 DPI).

These data were accompanied by ACE values of 94 mg/dL (8-52). Normocalcemia was not reached until corticotherapy begins, with a calcium levels of 11 mg/dl at the end of entry, and with 9.6 mg/dl calcium levels after two months of follow up with corticotherapy treatment. Same time renal function improvement and less proteinuria were observed (creatinine 2,3 mg/dl to 1,2 mg/dl, proteinuria 5g/24h to 3,2 g and albuminuria 3,5 g/24h to 2,3 g/24h) before treatment and after two months of follow up. Also, a decreased in adenopathies size was documented in new TC compared with first image study.

Discussion

Renal manifestations of sarcoidosis occur in up to 25-50% of all patients with diagnosis of sarcoidosis [1]. The most common form is the interstitial nephritis with or without the presence of granulomas. Glomerulonephritis has been described in association with sarcoidosis, being the most frequent forms reported MN, mesangiocapillary, focal sclerosis, IgA nephropathy and amyloidosis [2,3]. It is not clear if it is significant association because of a higher prevalence than expected of MN in these patients, but some authors believe it is a casual association based on the infrequency as a manifestation of sarcoidosis [4]. A CD4 TH1 mediated response occurs in sarcoidosis, while MN is related with immune-mediated LTH2 response by circulating antibodies that binds to an antigen express on glomerular podocytes surface [5].

It is believed that there is a genetic susceptibility that in addition with triggers develops the CD4 TH1 mediated response, the formation of granulomas and the macrophages and lymphocytes action. Cytokines produced in granulomas related to the TH1 response such TNFα, may alter glomerular membrane permeability favoring proteinuria [6,7]. There is an acceptable association with idiopathic MN cases and positive Ab-PLA2R determination (70-80%) [8,9]. In patients with sarcoidosis and MN have been documented cases related to negative and positive anti-PLA2R determination, this suggests that a detection of anti-PLA2R antibodies in serum or PLA2R antigen in biopsy should not be taken as evidence against a secondary cause [10,11].

Reviewing the literature, we have found another similar case of a male with a diagnosis of hypercalcemia secondary to sarcoidosis with pulmonary involvement and with a history of MN [12]. This patient presented a Grave’s disease coexisted. Thyrotoxicosis is being able to justify the hypercalcemia secondary to an increase in bone metabolism, but against what was expected in thyrotoxicosis, there were no levels of vitamin D suppressed. On the other hand, he had increased levels of calcium in urine unlike our patient, which can be explained by the usual treatment with thiazides in our case, and less calcium excretion due to the lower filtration rate secondary to the renal impairment.

Conclusion

To justify hypercalcemia, we need at least one of these two conditions, an increase in calcium intake through intestinal reabsorption or bone metabolism (probably secondary to the increased activity of the 1α-hydroxylase of granulomas), or a
lower renal calcium excretion rate, as could occur in patients with decreased glomerular filtration rate. Membranous Nephropathy is an uncommon manifestation associated with sarcoidosis. In patients with sarcoidosis and MN with precipitating factors, hypercalcemia could be more frequent secondary to an intrinsic predisposition.

Conflict of Interest

None of the authors declare have conflict of interest.

References