

Unusual Case of Severe Hypercalcemia and Diabetes Insipidus

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Citation

S Singh, A Rastogi, R Goyal, S Kumar, N Agrawal. *Unusual Case of Severe Hypercalcemia and Diabetes Insipidus*. The Internet Journal of Endocrinology. 2007 Volume 4 Number 2.

Abstract

We report a case of a 48 years old female presenting with polyuria, polydipsia, letharginess and weakness. She also had a history of exertional dyspnea, dry coughs and anti tubercular therapy 2 years back. Her routine biochemistry revealed markedly raised serum calcium levels. Correlating her respiratory symptoms with hypercalcemia, a granulomatous disorder was suspected. Serum angiotensin converting enzyme level (SACE) was elevated and histology (liver biopsy) confirmed the diagnosis of sarcoidosis. She was managed with intravenous fluids and oral steroids to which she responded within 7 days. After 2 months of follow up her calcium level was within normal limits and she is asymptomatic on 10 mg of prednisolone.

INTRODUCTION

Severe hypercalcemia is a rare clinical situation that presents with significant morbidity and success of treatment lies in identification of underlying cause. Though the causes of hypercalcemia are too many but hyperparathyroidism, malignant diseases and granulomatous disorders including sarcoidosis are among the commonest conditions encountered in clinical practice. Sarcoidosis is a chronic systemic disorder unknown etiology. The prime defect in sarcoidosis is the exaggerated cellular immune processes that include helper T cell 1 (T^H 1 cell) in particular. Clinical presentation of this disease is variable. We report a case of sarcoidosis presenting as polyuria, the cause of which was nephrogenic diabetes insipidus on account of hypercalcemia.

CASE SUMMARY

A 48 years female presented with polyuria, polydipsia, anorexia, weight loss, and nausea for 2 months. She had a history of exertional dyspnea, dry cough off and on and antitubercular treatment 2 years ago. She also had history of low backache for which she had received calcium and vitamin D in large doses. On examination, she was dehydrated, with pulse rate of 100 /minute and blood pressure 120/80 mm of Hg with hepatosplenomegaly. Her laboratory findings were as follows - hemoglobin 10.1 gm%, total leukocyte count 5,550/cmm, differential leukocyte count - polymorph 78%, lymphocytes 19%, monocytes 1%, eosinophil 2%; alanine aminotransferase (ALT) 36 IU/L,

aspartate aminotransferase (AST) 19IU/L, Serum protein 8.5 gm/dl, albumin- 4 gm/dl, Serum alkaline phosphatase 918 IU/L (raised), fasting and post oral glucose challenge plasma glucose values 88.2mg/dl and 140 mg/dl respectively, serum total calcium 14.6mg/dl (raised), serum phosphate 4.1mg/dl, urea 63.5 mg/dl, creatinine 3.8 mg/dl, serum Na⁺ 141.3meq/L, K⁺ 4meq/L, 24 hour urinary calcium 990 mg/day, serum iPTH- 14.3pg/ml (reference value 15-65). Serum angiotensin converting enzyme (SACE) level was 158 U/L (Reference value 8 – 65). QTc interval in electrocardiogram was 0.40sec. Roentgenogram of chest showed reticulonodular pattern in upper zone bilaterally. USG abdomen showed hepatosplenomegaly. CT thorax revealed characteristic changes (figure 1a, 1b).

Figure 1

Figure 1a: CT THORAX diffuse reticulonodular shadows in bilateral lung fields

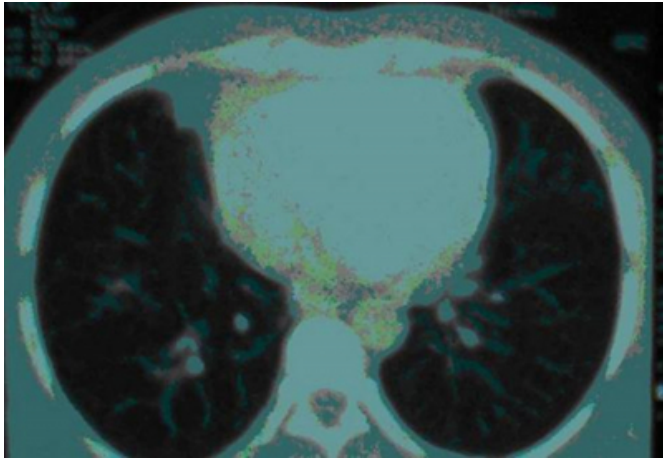
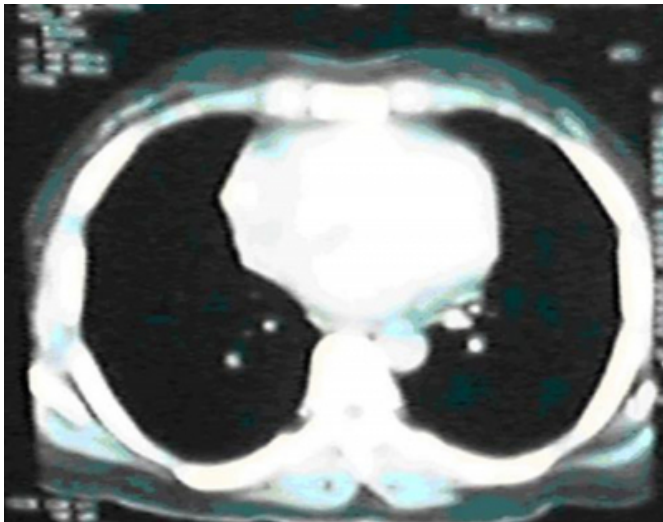


Figure 2

Figure 1b: CT THORAX bilateral calcified hilar, pretracheal, carinal and subcarinal lymph nodes



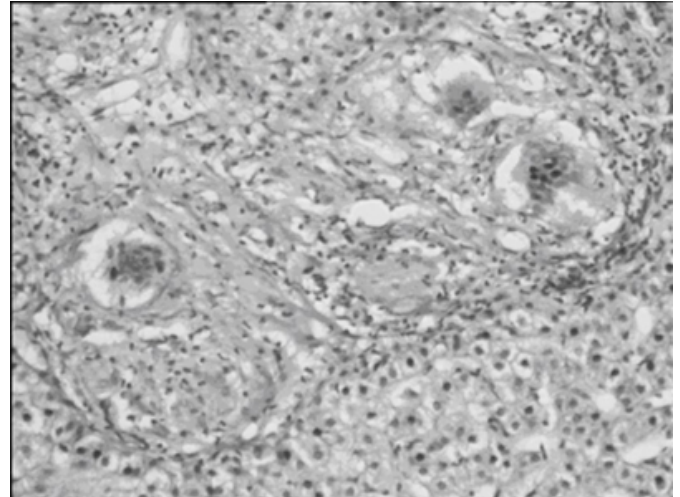
Bronchoscopy showed generalized small nodular lesions in the bilateral tracheobronchial tree with mucosal hyperemia with out intraluminal growth. Bronchoalveolar lavage and iliac crest bone marrow aspiration were non conclusive. Histological confirmation was done by liver biopsy (figure 2)

She was diagnosed to be a case of Sarcoidosis complicated by severe hypercalcemia leading to nephrogenic diabetes insipidus. Patient was adequately hydrated with intra venous fluids for the initial 4 days with subsequent addition of oral steroid (prednisolone 40 mg/day). The symptoms, renal function and serum total calcium improved with the ongoing therapy. She was discharged on 10 mg prednisolone. She

was advised to take plenty of fluids, avoid sun exposure and restrict calcium /vit D intake.

Figure 3

Figure 2: HISTOLOGY OF LIVER multiple non-caseating epithelial cell granulomas without lymphocytic mantle (H & E STAIN) magnification X 100



DISCUSSION

The crucial aid in the diagnosis of the presenting case includes clinical profile, treatment history, past history and subsequent investigations. Most distressing symptoms were polyuria, nocturia and polydipsia due to hypercalcemia and renal tubular defect. The initial test in the work up for the cause of hypercalcemia is intact PTH level. Low iPTH level in the presence of hypercalcemia ruled out primary hyperparathyroidism. In view of the symptoms of hypercalcemia with organomegaly, respiratory symptoms with low serum iPTH level, possibility of lymphoproliferative disorder or granulomatous disease was considered. The abdominal ultrasound and chest x ray were non supportive. CT thorax revealed diffuse reticulonodular shadows in bilateral lung fields (fig 1 a) with bilateral calcified hilar, pretracheal, carinal and subcarinal lymph nodes (fig 1 b). These findings were suggestive of sarcoidosis. Three times raised serum ACE activity further supported the diagnosis. The serum ACE level is also raised in lymphoproliferative disorders, fungal infection, leprosy, silicosis, tuberculosis and hypersensitivity pneumonitis but such high level is found in sarcoidosis ^{2,3}. Bronchoalveolar lavage may help in the diagnosis ⁴ however it was non conclusive in our case. The gold standard test for diagnosing sarcoidosis is transbronchial lung biopsy ⁵ which was deferred due to hyperemic bronchial mucosa. Liver biopsy is usually not done for the diagnosis ⁶ but we were to resort to

it due to failure of other diagnostic tests. It showed multiple non-caseating epithelial cell granulomas without lymphocytic mantle.

Harrel et al ⁷ first described the association between sarcoidosis and hypercalcemia. The mechanisms leading to hypercalcemia in sarcoidosis are ectopic activity of 1 α -hydroxylase enzyme ⁸ and expression of PTHrP gene in granuloma ⁹. Life threatening hypercalcemia is uncommon in sarcoidosis ¹⁰. However it may worsen with excessive calcium/vitamin D intake and sun exposure ¹¹. Our patient had history of vitamin D therapy and this could have precipitated severe hypercalcemia.

Polyuria in sarcoidosis can also be a manifestation of central diabetes insipidus due to involvement of hypothalamic - pituitary axis ¹². In our patient history of failed response to desmopressin therapy ruled out the possibility of central DI.

Steroids have a major role in the management of symptomatic hypercalcemia complicating sarcoidosis ¹³. The patient was started on tablet prednisolone 40 mg / day with gradual tapering. The mechanisms by which steroid acts are by inhibiting extrarenal 1 α -hydroxylase activity ¹⁴, down regulating TNF α /IL6 expression thereby decreasing PTHrP production ¹⁵, inhibiting gastrointestinal calcium absorption and lastly by decreasing osteoclastic activity thereby promoting hypercalciuria. It causes a gradual decrease in serum calcium within 2–4 days and reduction in urinary calcium excretion soon follows, within 7–10 days. Prednisolone dosage can be reduced over a period of 4–6 weeks. Long-term follow up requires 24-hour urinary calcium levels, bone mineral density measurement and USG abdomen if renal dysfunction exists.

CONCLUSION

Hypercalcemia has variable presentation in clinical practice. A high level of suspicion must be kept in dealing with patients with polyuria, letharginess and dehydration. Initial evaluation of hypercalcemia requires assay of intact PTH in serum. Granulomatous disorders should be considered in the work up of hypercalcemia with suppressed iPTH. Sarcoidosis needs to be screened by radioimaging of chest, abdominal ultrasound and serum angiotensin converting

enzyme level in serum. Detailed clinical evaluation and relevant investigations lead to definitive diagnosis and specific measures taken to correct hypercalcemia can prevent life threatening situation.

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