DOI: 10.7860/JCDR/2016/16770.7783

Case Report

Internal Medicine Section

Schimidt Syndrome: An Unusual Cause of Hypercalcaemia

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ABSTRACT

Autoimmune polyglandular syndrome type 2 also known as Schmidt syndrome. It is a rare disorder involving a combination of Addison's disease with autoimmune thyroid disease with or without type 1 diabetes mellitus. In this case report one such patient with this rare syndrome is described who presented with hyperpigmentation of knuckles, palms and soles with significant weight loss for 2 months. At presentation she also had severe hypercalcaemia. Severe hypercalcaemia is rare and hypercalcaemia at the initial presentation of Addison's disease is also unusual. The mechanism of hypercalcaemia in addisons and management of this patient is discussed.

Keywords: Autoimmune polyendocrinopathies, Hypercalcaemia, Hypocortiolism

CASE REPORT

A 36-year-old lady presented to the outpatient department with loss of appetite and significant loss of weight since 2 months. In addition she had noticed a darkening of her skin colour over the same period [Table/Fig-1]. There were recurrent episodes of vomiting at the time of presentation.

On examination, she was emaciated with hyperpigmentation over her palms and soles [Table/Fig-2]. Rest of the examination was normal. There was no vitiligo or alopecia.

[Table/Fig-1]: Patient showing darkening of the skin colour.
[Table/Fig-2]: Hyperpigmentation over palms.

Since she had presented with the clinical phenotype of Addison's disease, we had sent an 8am cortisol value which was low at 4.1microgm/dl and then proceeded to do an ACTH stimulation test which showed a poor stimulation of the adrenals to ACTH confirming adrenal insufficiency. Baseline ACTH levels ([Table/Fig-3] Laboratory values) were found to be elevated excluding a pituitary cause for hypoadrenalism. CT abdomen was obtained which showed normal adrenal gland morphology with no local masses or infectious pathology (like tuberculosis or histoplasmosis) causing hypoadrenalism. Once Addison's disease had been demonstrated, a search for other autoimmune diseases which are commonly encountered with the same such as thyroid disorders, B12 deficiency and vitiligo was undertaken. Of these only automimmune thyroiditis was present.

Her TSH was supressed with an elevated T4 value. Antithyroid peroxidase antibodies, which are high is hashimotos thyroiditis, were very high. Thyroid uptake study was also done which showed a low uptake suggestive of thyroiditis. Her B12 assay and pernicious anaemia antibody screen were also done, these were normal and negative respectively.

Her laboratory investigations showed a corrected calcium value of 12.4mg/dl (severe hypercalcaemia). To evaluate the hypercalcaemia further, Parathyroid hormone, Phophorous and Vitamin D were done [Table/Fig-3]. Her phophorous and parathyroid hormone values were normal and vitamin D was low. Extensive paraneoplastic screening was also undertaken to look for evidence of PTHrP (PTH related protein) related hypercalcaemia. This search included CT imaging of the thorax and abdomen along with a bone marrow examination and cervical cancer screening. These were negative for malignancy. Since other causes had been ruled out, hypercalcaemia was most likely due to hypocortisolism.

She had come with features of an adrenal crisis and severe hypercalcaemia. Hence she was aggressively hydrated to bring down the calcium and started on Hydrocortisone and 100mg every 8 hours to overcome the crisis after an initial bolus dose of 200mg was given. With this her calcium came down to normal limits. For the thyroiditis she was started on Propranolol and kept on follow up. At discharge she was on a maintenance dose of prednisolone.

At review 3 months later, she had gained weight with no further vomiting. Her electrolytes, calcium and phosphorous were normal.

Lab Parameter	Patient value	Reference range
8 am cortisol	4.1 microgram/dl	5-15micgm/dl
ACTH post stimulation with 1mg dexa	5.1micgm/dl	18micgm/dl
ACTH value baseline	572pg/dl	0-46pg/ml
TSH	<0.004miclU/ml	2-5miclU/ml
T4	15.1microgram/dl	8-12micgm/dl
fTc	1.92micgm/dl	0.8-2micgm/dl
Anti TPO antibodies	721 IU/ml	50 IU/ml
Calcium corrected	12.4mg/dl	8-10mg/dl
Phosphorous	2.3mg/dl	2-5mg/dl
Parathyroid hormone	15.8 pg/ml	8-74 pg/ml
Vitamin D	5.69	>30
Fasting blood sugar	82mg/dl	70-110mg/dl
Post prandial blood sugar	130mg/dl	110-140mg/dl

[Table/Fig-3]: Laboratory values.

DISCUSSION

Autoimmune polyglandular syndrome type 2 is an uncommon disorder with a prevalence of 1.4 to 1.45 per 100,000 persons [1]. Type 2 polyglandular syndrome represents the combination of Addison's disease (the pivotal disease) along with autoimmune thyroid disease. This is also labelled- the Schimidt syndrome. When type 1 diabetes mellitus is also present, it is known as the Carpenter's syndrome. There maybe other minor diseases such as vitiligo, hypergonadotropic hypogonadism, chronic autoimmune hepatitis, alopecia, pernicious anaemia and myasthenia gravis associated with this syndrome.

This autoimmune disorder appears to have a higher prevalence in middle aged women [2]. Among a series of 129 patients with this syndrome, it was found that the most common combination of disorders was Addison's, Hashimotos' thyroiditis in 88.4% of people, while the least common was Addison's, graves disease and type 1 diabetes seen in only 11.6% of individuals [3].

Pathogenesis has been lined to both humoral and cellular immunity. The autoantibodies to the adrenal cortex and 21 hyroxylase prove an immune mechanism. The cellular component of the same is proven with lymphocytic infiltrates within the thyroid tissue and adrenals on biopsy of respective organs. There seems to also be a genetic susceptibility to these diseases with certain HLA types such as DRB1*04; DQA1*03; DQB1*0302 and DRB1*03; DQA1*0501; DQB1*02 being independently more associated with the disease independent from their association with just type 1 diabetes [4].

Hypercalcaemia is almost as common as hyponatraemia in addison's disease. However life threatening hypercalcaemia is rare and usually is associated with only parathyroid disorders or their treatment [5]. Hypercalcaemia as a presenting feature of Addison's disease is also unusual. It has been described in both primary as well as secondary causes of adrenal insufficiency like sepsis [6].

Many theories have been proposed to explain why there is hypercalcaemia in patients with adrenal insufficiency. One theory is that there is an increases calcium resorption from the bones. This has been supported by findings of increased urinary hydroxyproline secretion. Another theory is that the influx of calcium is due to a decrease in stanniocalcin production. Stanniocalcin is a paracrine hormone produced from the adrenals which normally decreases calcium absorption from the intestine and increases urinary excretion of the same [7].

In patients with hypercalcaemia it is more important to rule out other causes of hypercalcaemia such as lymphomas, sarcoidosis and tumour induced hypercalcaemia due to PTH related peptide. These were ruled out in this patient by CT of her thorax and abdomen, blood PTH estimation and bone marrow studies which were normal.

CONCLUSION

Addison's disease can rarely produce severe hypercalcaemia, although other causes of hypercalcaemia such as hyperparathyroidism and malignancy need to be ruled out before attributing hypercalcaemia to adrenal insufficiency. In a patient with hypoadrenalism it is important to look for other associated diseases such as thyroiditis, B12 deficiency and vitiligo. Hypoadrenalism can produce the hypercalcaemia through multiple mechanisms.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 12, 2015**
Date of Peer Review: **Nov 4, 2015**
Date of Acceptance: **Dec 11, 2015**
Date of Publishing: **May 01, 2016**