CASE REPORT

TWO CONCOMITANT ENDOCRINOPATHIES CAUSING HYPERCALCEMIA IN SHEEHAN SYNDROME

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ABSTRACT

The objective of this study is to report a case of hypercalcemia secondary to two concomitant endocrinopathies. The case included a 34-year-old woman presented for nausea, vomiting, diarrhea and depression and found to have moderate hypercalcemia and hyperphosphatemia on laboratory tests. She was diagnosed with acute central adrenal insufficiency due to Sheehan syndrome, associated with hyperthyroidism secondary to overtreatment by thyroid hormones. She was successfully managed with hydration, stopping levothyroxine, and glucocorticoids with total resolution of her symptoms and normalization of calcium level. Central adrenal insufficiency and hyperthyroidism are rare causes of hypercalcemia and only few cases combine these 2 endocrine disorders.

Key words: Histopathology, Senga sp., Channa striatus, Mucosa, Intestinal tissue and Villi.

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INTRODUCTION

Many reports presented cases of hypercalcemia due to adrenal insufficiency or hyperthyroidism. To our best knowledge, cases of Sheehan syndrome and iatrogenic hyperthyroidism presented with hypercalcemia have not been reported in the literature before. Herein, we describe a rare case combining these 2 conditions with moderate calcium elevation.

Case presentation

A 34 year old woman, presented to the emergency department for nausea, vomiting and diarrhea. History goes back to 3 weeks prior to presentation, when she started complaining of sore throat, fever and epigastric pain relieved by vomiting. She took a full course of augmentin (amoxicillin-clavulanate 7days) for a diagnosis of pharyngitis, but she didn’t ameliorate, so she was admitted to the infectious disease department for investigation.

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She has a history of rheumatic heart disease, on biological valve, operated 3 years ago, an abortion since 6 years ago, an abortion since 6 years ago, an abortion since 6 years ago. She delivered a healthy baby boy by an uneventful C-section 7 months ago with an Apgar score of 9/10. Vital signs upon admission were stable. No hypotension, no hypoglycemia. Laboratory tests showed a normal leukocyte count of 5600/mL (4500-11000), anemia with an hemoglobin of 11g/dl (12-15.5), in addition to marked hypercalcemia and hyperphosphatemia (Calcium level of 12.8 and phosphate of 5.84). While investigating the etiology of these electrolytes disturbances, abdominal ultrasound was done and was unremarkable. Table 1 presented the metabolic workup:

Patient started on intravenous hydration (3 litres daily) and levothyroxine was stopped, but the diarrhea didn’t resolve. Calcium level decreased to a maximum level of 10.82 mg/dl after 3 days of hydration. After a detailed history, patient reported weight loss of 10 kilograms after her delivery, depression, loss of appetite, failure of lactation and menstrual irregularities 2 months postpartum. Thus, 8 am cortisol level was taken and revealed an extremely low value of 0.386 mg/dl.
Thyroid function tests reviewed 3 months ago, when euthyrox was initiated, demonstrated central hypothyroidism with a TSH and FT4 of 1.77 (0.27-4.2 mIU/ml) and 0.688 (0.93-1.7) ng/dl respectively. Intravenous stress dose of steroids was given (initial dose of hydrocortisone 100 mg intravenous then every 8 hours). And hormonal workup confirmed hypopituitarism (Table 2). MRI pituitary showed a small gland measuring 17 x 6 x 2 mm (transverse x antero-posterior x height) with areas of old patchy necrosis (Images 1 and 2). The diagnosis of Sheehan syndrome with central adrenal insufficiency, hypercalcemia, and anemia of chronic disease was established. Patient experienced rapid resolution of her illness with hazardous amelioration of her depression mainly, calcium level returned to normal (8.76 mg/dl) 2 days after initiation of steroids. She was discharged on prednisone 5 mg twice daily. Follow up FT4 showed a low level of 0.7 ng/dl after 1 month so levothyroxine was resumed at a dose of 50 mcg daily.

**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th>Values</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>12.8</td>
<td>8.5-10.5 mg/dl</td>
</tr>
<tr>
<td>Albumin</td>
<td>4</td>
<td>3.5-5.5 g/dl</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>5.84</td>
<td>2.5-4.5 mg/dl</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2.14</td>
<td>1.58-2.55 mg/dl</td>
</tr>
<tr>
<td>25-hydroxvitamin D</td>
<td>35</td>
<td>20-30 ng/ml</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>3.35</td>
<td>15-65 pg/ml</td>
</tr>
<tr>
<td>Free Thyroxine</td>
<td>3.94</td>
<td>0.93-1.7 ng/dl</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>34</td>
<td>7-56 IU/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>28</td>
<td>5-40 IU/L</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>62</td>
<td>44-147 IU/L</td>
</tr>
<tr>
<td>GOT</td>
<td>21</td>
<td>9-48 IU/L</td>
</tr>
<tr>
<td>Lipase</td>
<td>30</td>
<td>13-60 IU/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>137</td>
<td>135-145 mEq/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.08</td>
<td>3.5-5 mEq/L</td>
</tr>
<tr>
<td>Folate</td>
<td>&gt;20</td>
<td>3.89-26.8 ng/ml</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>2000</td>
<td>13-150 ng/ml</td>
</tr>
<tr>
<td>Ferritin</td>
<td>377</td>
<td>13-150 ng/ml</td>
</tr>
<tr>
<td>Iron</td>
<td>45</td>
<td>37-145</td>
</tr>
<tr>
<td>TIBC</td>
<td>144</td>
<td>274-385</td>
</tr>
<tr>
<td>Iron saturation</td>
<td>31</td>
<td>20-50%</td>
</tr>
<tr>
<td>ASO titer</td>
<td>482</td>
<td>0-200</td>
</tr>
</tbody>
</table>

**Table 2.**

<table>
<thead>
<tr>
<th></th>
<th>Values</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>6.52</td>
<td>10-50 pg/ml</td>
</tr>
<tr>
<td>cortisol</td>
<td>0.386</td>
<td>6-18.4 (morning)</td>
</tr>
<tr>
<td>FT4</td>
<td>3.94</td>
<td>0.27-1.7 ng/dl</td>
</tr>
<tr>
<td>FSH</td>
<td>13.64</td>
<td>4.5-21.5 IU/L</td>
</tr>
<tr>
<td>LH</td>
<td>15.12</td>
<td>14.95-6 IU/L</td>
</tr>
<tr>
<td>estradiol</td>
<td>6.46</td>
<td>41-398 pg/ml</td>
</tr>
<tr>
<td>prolactin</td>
<td>76.37</td>
<td>4.79-23.3 ng/ml</td>
</tr>
<tr>
<td>IGF1</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Adrenal insufficiency can be either primary or secondary. Sheehan syndrome is among the central causes of adrenal insufficiency. It is an ischemic pituitary gland necrosis secondary to hemorrhage peri and postpartum leading to hypopituitarism. It is more prevalent in developing countries where obstetric care is still poor. Pituitary is a highly vascularized organ, doubling in volume during pregnancy due to lactotroph cells hyperplasia. Thus, it is more vulnerable to ischemia resulting in central adrenal failure (Tirupati et al., 2013). Presentation of hypoadrenalism is variable. Symptoms and signs of secondary adrenocortical insufficiency are nonspecific and diagnosis may be difficult (Harano et al., 2015). It can be manifested as hypotension, hyponatremia, hyperkalemia, hypoglycemia, as well as hypercalcemia (Nair). The relationship between calcium metabolism and adrenal glands was first described by Guleke in 1911 (Walser et al., 1963). It occurs not only in primary adrenal insufficiency, but also in central hypoadrenalism, however it is more severe in the primary form (Nair; Ozkaya et al., 2015). 5.5% of the patients with primary adrenal insufficiency have hypercalcemia whereas the prevalence in central adrenal insufficiency is still unclear (Harano et al., 2015). Generally, the differential diagnosis of hypercalcemia includes primary hyperparathyroidism, malignancy (with or without parathyroid hormone-related protein [PTH-rp]), hypervitaminosis D (secondary to granulomatous diseases or other causes), parenteral nutrition, thyrotoxicosis, immobilization, critical care hypercalcemia. Administration of steroids lowers calcium value except hypercalcemia secondary to hyperparathyroidism which may require large doses. It does not affect the level in normal patients (Walser et al., 1963). Malignancy accounts for the majority (70%) of hypercalcemic cases followed by primary hyperparathyroidism (in 20%). Other causes like granulomatous diseases, drugs, thyrotoxicosis, milk-alkali syndrome, and immobilization lead to hypercalcemia in 10%. Adrenal insufficiency is rare, causing mild to moderate hypercalcemia (Sakao et al., 2014). In this case, persisted elevated calcium level despite hydration and the withdrawal of
levothyroxine is a pitfall to make the diagnosis challenging and to consider other causes of hypercalcemia. In a case of hypercalcemia unresponsive to fluid replacement, we recommend ruling out adrenocortical insufficiency among other common diseases like malignancy, hyperparathyroidism, hyperthyroidism, and vitamin D intoxication (Harano et al., 2015). In our case, the intact PTH level was low, ruling out primary hyperparathyroidism, and the patient had high phosphorus level eliminating PTH or PTH-rp as causes of hypercalcemia, that generally induce phosphaturia and subsequently low to low-normal phosphorus level. In front of hypercalcemia and hyperphosphatemia, hypervitaminosis D was on the top of diagnosis, but this level (35g/dl) rarely lead to these electrolytes disturbances. There is no evidence of parenteral nutrition or any formula containing calcium and vitamin D. Critical care hypercalcemia is typically mild and associated with mild increases in PTH levels. These features are absent in our case, and hypercalcemia is moderate. Herein, immobilization was not present to explain hypercalcemia. Moreover, the case patient had a history of central hypothyroidism treated with an excess of thyroid hormones, and her thyroid function test showed overtreatment (FT4 2.3 times the upper limit of normal) that could exacerbate the hypercalcemia, present in adrenal insufficiency, resulting in this high serum calcium level. Because of the low metabolism present in adrenal insufficiency, overtreatment by levothyroxine may happen. Thus, the hypercalcemia in our case was probably secondary to an adrenal insufficiency and iatrogenic hyperthyroidism. Hyperphosphatemia, present in our patient, can also support the diagnosis of adrenal insufficiency (Lee and Twigg, 2015). Hypercalcemia was seen in one-fifth of hyperthyroid cases, and was usually mild. The mechanism is not completed investigated, but it is generally due to mobilization of calcium from bone and increase in bone turnover leading to high levels of serum alkaline phosphatase mostly of bone origin. The hypermetabolism and high interleukin-6 levels may contribute also (Ozkaya et al., 2015). Symptoms of hyperthyroidism may be masked by those of hypercalcemia. Excess thyroid hormones per se may produce a relative adrenal insufficiency due to acceleration of metabolism, increasing further the hypercalcemic state (Ozkaya et al., 2015). This moderate hypercalcemia presented here was due to the concomitant effect of hyperthyroidism and adrenal insufficiency.

Severe hypercalcemia which developed following adrenalectomy was prevented by simultaneous thyroidectomy and starting levothyroxine in Addison’s disease exacerbates the hypercalcemic state. All these features demonstrate that thyroid hormones are important in the appearance of hypercalcemia in adrenal failure (Ozkaya et al., 2015). In our case, iatrogenic hyperthyroidism stimulates adrenal insufficiency and both act in a synergistic way to aggravate the hypercalcemia. Therefore, it is important to consider the coexistence of these 2 endocrinopathies as causes of hypercalcemia. Thyroid hormones and steroids are important in regulating calcium homeostasis (Ozkaya et al., 2015). Hypercalcemia is an infrequent complication of adrenal insufficiency. The exact mechanism underlying this hypercalcemia is unknown. In adrenal insufficiency, decrease in calcium excretion by the kidneys is the first explanation of hypercalcemia. Administration of glucocorticoids increase calcium excretion in urine and this increase falls with the reduction in plasma calcium. Thus, the role of kidney as part of hypercalcemia in adrenal insufficiency may be a possibility (Walser et al., 1963). Hypovolemia and decrease in the glomerular filtration rate (GFR) can reduce the level of calcium filtered at the glomerulus, and can increase proximal tubular reabsorption leading to hypercalcemia. Volume repletion normalize the low GFR and the level of filtered calcium but does not reverse the increased input of calcium into the circulation (Sakao et al., 2014). Urinary hydroxyprolinea a marker used for bone resorption. It can be elevated in patient with hypercalcemia secondary to cortisol deficiency. Thus, this suggest that increased bone resorption is another mechanism responsible for hypercalcemia in patients with adrenal insufficiency (Sakao et al., 2014). Calcium may also be released from bone in patients with adrenal insufficiency via decreasing bone remodeling in the trabecular bone surfaces, accelerating nontrabecular bone resorption or increasing calcium transport out of the interstitial bone fluid by quiescent lining cells (Nair).

In bone, there is also glucocorticoid receptors. It has been also suggested that in adrenal insufficiency, bone is thyroxine dependent, and hypercalcemia can develop only in the presence of thyroid hormone. This mechanism could explain the hypercalcemia in our case (Nair). Increase in calcium absorption from the gastrointestinal tract is an unlikely mechanism, as there is a similarity in calcium level between calcium-rich and calcium free-diets in adrenalectomized dogs (Nair). However, increase in 1-alpha-hydroxylase activity, and then in calcitriol leading to increased intestinal absorption of calcium have been identified as prednisone inhibits this enzyme activity, thus reducing hypercalcemia (Ahn et al., 2016). Adrenal insufficiency can decrease stanniocalcin, a paracrine hormone secreted from the adrenal gland, that reduce circulating calcium levels. Deficiency in this adrenal hormone increases skeletal calcium efflux into circulation and results in hypercalcemia (Ahn et al., 2016; Katsnelson et al., 2012). Symptoms of adrenal insufficiency and hypercalcemia are not specific, and may mimic those of critical illness (Lee, 2015). Nausea, vomiting and abdominal pain may be due to hypercalcemia or adrenal insufficiency, but weight loss, and depression postpartum are more common in adrenal insufficiency. In front of hypercalcemia and critical illness, adrenal insufficiency should be suspected especially if the cause is unclear and it is confirmed generally by ACTH stimulation test (Nair). In our case, this test was not performed, and the diagnosis of adrenal insufficiency was established by extremely low morning cortisol level.

The resolution of hypercalcemia by hydration and glucocorticoids support this diagnosis (Nair). After drawing blood samples for measurement of electrolyte, glucose, plasma cortisol, and ACTH levels, critically ill, unstable patients should receive immediately stress dose of glucocorticoids (Nair). Hydrocortisone 100 mg intravenous bolus initially, followed by 100 mg every 6 hours, may be used. Dexamethasonehas the advantage of little or no interference with the measurement of cortisol if blood withdrawal cannot be performed immediately before the stress dose. Dextrose should also be given in hypoglycemic patients in addition to isotonic saline (Nair). The cause of hypoadrenalism should be established. If primary adrenal insufficiency was the underlying cause, patients generally required mineralocorticoid replacement. Hypercalcemia will resolve after glucocorticoid therapy. The steroid dose should be tapered in the following days if the patient is hemodynamically and clinically stable (Nair).
Conclusion

Hypercalcemia should always be suspected as a sign of adrenal insufficiency, in a critically ill patient. Usually, we should not wait for the laboratory tests if the clinical suspicion is high. Identification of the hypoadrenalism is extremely important as well as starting glucocorticoids.

REFERENCES


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