



ISSN: 2319-9490

## CASE REPORT

### TWO CONCOMITANT ENDOCRINOPATHIES CAUSING HYPERCALCEMIA IN SHEEHAN SYNDROME

<sup>1,2,\*</sup>Carine Ghassan Richa, <sup>3</sup>Afaf Michel Minari, <sup>1,4</sup>Salwa Nassif Azar, <sup>1,5</sup>Mohamad Souheil EL Rawas and <sup>1,6</sup>Akram Salim Ehtay

<sup>1</sup>Department of Endocrinology, Rafic El Hariri University Hospital, Beirut, Lebanon

<sup>2</sup>Endocrinology fellow, Lebanese University, Hadath, Lebanon

<sup>3</sup>Infectious disease department, Rafic El Hariri University Hospital, Beirut, Lebanon

<sup>4</sup>Endocrinology fellow, Lebanese University, Hadath, Lebanon

<sup>5</sup>Endocrinologist, Rafic El Hariri University Hospital, Beirut, Lebanon

<sup>6</sup>Head of Endocrinology and Internal Medicine departments, Rafic El Hariri University Hospital, Beirut, Lebanon

Received 20<sup>th</sup> July, 2018; Accepted 17<sup>th</sup> August, 2018; Published 30<sup>th</sup> September, 2018

#### 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.

**Copyright © 2018, Carine Ghassan Richa et al.** This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Citation:** Carine Ghassan Richa, Afaf Michel Minari, Salwa Nassif Azar, Mohamad Souheil EL Rawas and Akram Salim Ehtay, 2018. "Histopathological changes caused by *Senga sp.* In *Channa striatus*" *International Journal of Current Research in Life Sciences*, 7, (09), 2696-2699.

#### 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.

She has a history of rheumatic heart disease, on biological valve, operated 3 years ago, an abortion since 6 years secondary to an abdominal trauma after a fall, vitamin D deficiency on maintenance dose (10000 IU weekly), hypothyroidism on levothyroxine 50 mcg daily. 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.

\*Corresponding author: <sup>1,2</sup> Carine Ghassan Richa,

<sup>1</sup>Department of Endocrinology, Rafic El Hariri University Hospital, Beirut, Lebanon.

<sup>2</sup>Endocrinology fellow, Lebanese University, Hadath, Lebanon.

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 hazardeous amelioration of her depression mainly, calcium level returned to normal (8.76mg/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.

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

Table 2.

	Values	Normal range
ACTH	6.52	10-50 pg/ml
cortisol	0.386	6-18.4 (morning)
FT4	3.94	0.93-1.7 ng/dl
FSH	13.84	4.5-21.5 IU/L
LH	15.12	14-95.6 IU/L
estradiol	6.46	41-398 pg/ml
prolactin	76.37	4.79-23.3 ng/ml
IGF1	NA	NA

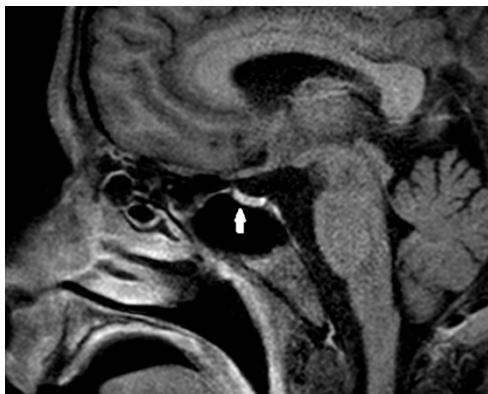


Figure 1. Brain magnetic resonance imaging of pituitary gland. T1 3D Sagittal view + contrast showing areas of necrosis (heterogeneous enhancement)



Figure 2. Brain magnetic resonance imaging of pituitary gland. T1/TSE Coronal dynamic view + contrast showing the necrosis

## 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 (35ng/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 completely 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 hydroxyproline is 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 more 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. Dexamethasone has 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

- Ahn SW, Kim TY, Lee S, Jeong JY, Shim H, Han Y min, et al. 2016. Adrenal insufficiency presenting as hypercalcemia and acute kidney injury. *Int Med Case Rep J.*, 29; 9:223–6.
- Harano Y, Kitano A, Akiyama Y, Kotajima L, Honda K, Arioka H. 2015. A case of isolated adrenocorticotrophic hormone deficiency: a rare but possible cause of hypercalcemia. *Int Med Case Rep J.*, 27;8:77–9.
- Katsnelson S, Cella J, Suh H, Charitou MM. 2012. Hypercalcemia in a patient with autoimmune polyglandular syndrome. *Clin Pract [Internet]*, 4 [cited 2018 Sep 5];2(2). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981294>.
- Nair GKV, Simmons DL. Adrenal Insufficiency Presenting as Hypercalcemia. :4.
- Lee AS, Twigg SM. 2015. Opioid-induced secondary adrenal insufficiency presenting as hypercalcaemia. *Endocrinol Diabetes Metab Case Rep [Internet]*, [cited 2018 Sep 5]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4496564/>
- Ozkaya HM, Keskin FE, Haliloglu OA, Senel TE, Kadioglu P. 2015. Life-Threatening Hypercalcemia due to Graves' Disease and Concomitant Adrenal Failure: A Case Report and Review of the Literature. *Case Rep Endocrinol.*, 1–5.
- Sakao Y, Sugiura T, Tsuji T, Ohashi N, Yasuda H, Fujigaki Y, et al. 2014. Clinical Manifestation of Hypercalcemia Caused by Adrenal Insufficiency in Hemodialysis Patients: A Case-series Study. *Intern Med.*, 53(14):1485–90.
- Tirupati, E S, D R, G R, P S, V S, et al. 2013. Sri Venkateswara Institute of Medical Sciences, Sheehan's syndrome: A single centre experience. *J Clin Sci Res.*, 1;16–21.
- Walser M, Robinson BHB, Duckett JW. 1963. The hypercalcemia of adrenal insufficiency. *J Clin Invest.*, 1;42(4):456–65.
- gr100025.pdf [Internet]. [cited 2018 Sep 5]. Available from: <http://www.grandroundsjournal.com/articles/gr100025/gr100025.pdf>

\*\*\*\*\*