

INTRODUCTION

Adrenal Insufficiency is an uncommon, but treatable cause of hypercalcemia.

CASE SUMMARY

History of Present Illness

A 57-year old Caucasian female with a 2 year history of progressively worsening nausea, vomiting, and weakness was found to have a calcium level of 12.9. Episodes of vomiting initially occurred approximately once per month, but had progressed to a daily occurrence during the last six months. Emesis was nonbilious and nonbloody. She noted decreased PO intake and a fifty pound weight loss during that time. She noted feeling "weak and lightheaded" for many months. She noted vague mid-epigastric pain for the last month. She had previously undergone an extensive workup for her symptoms, including MRI of brain, CT of abdomen, pelvis, and colonoscopy/endoscopy, which had not yielded a diagnosis.

Past Medical History: Chronic nausea, vomiting, weakness of unclear etiology

Meds: Omeprazole 20mg PO BID, Promethazine 12.5mg PO q6 PRN

Social History: No tobacco, alcohol, drugs. Lives with husband.

Family History: Mother—type II diabetes mellitus

Pertinent Physical Exam

- Vital Signs: Afebrile, BP 118/68, HR 99, RR 18. No orthostasis.
- General: No acute distress. Chronically ill appearing. No hyperpigmentation.
- Neck: No thyromegaly. No lymphadenopathy.
- Abdomen: Soft, nontender, nondistended. No masses.
- Extremities: No edema, clubbing, cyanosis.

Laboratory/Radiological Data

- Calcium 12.9, Ionized Calcium 6.14**, Phos 3.9, Albumin 3.8
- Sodium 130**, Potassium 4.3, Bicarbonate 23, Creatinine 1.3
- PTH-I < 3** (10-65)
- FSH, LH, Prolactin, TSH, IGF-1 normal
- Vitamin A, PTH-rp, 1-25 Dihydroxy Vitamin D, 25-OH Total Vitamin D 17, SPEP, UPEP, CEA, CA 19-9 normal
- Mammogram, CT Chest, Abdomen, Pelvis, MRI brain normal
- AM Cortisol **0.9**
- Cosyntropin Stimulation Test: **0.9, 1.0, 1.0**
- ACTH **1373 (5-27)**

Clinical Course

- The patient was diagnosed with primary adrenal insufficiency, most likely idiopathic vs. autoimmune.
- Started on replacement dose hydrocortisone with significant improvement in nausea, vomiting, dizziness, hypercalcemia.
- Hyponatremia gradually improved with titration of hydrocortisone.

FIGURES

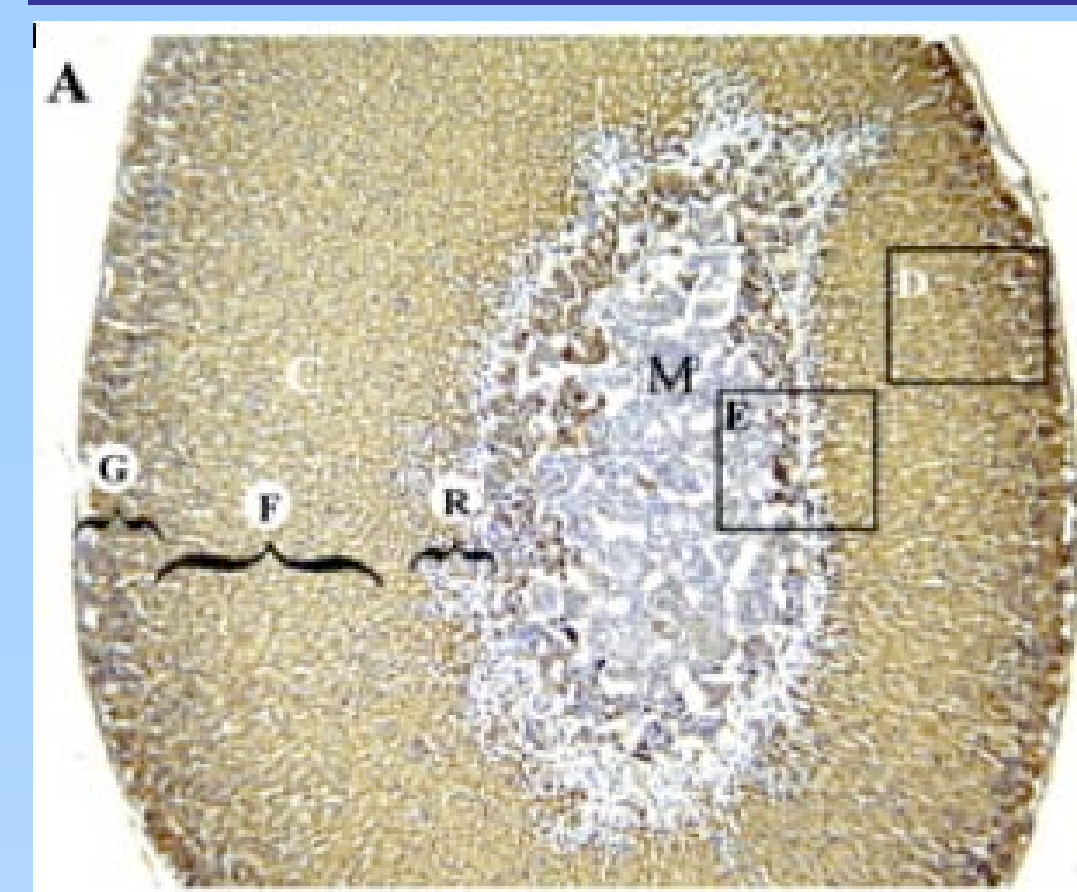


Figure 1A: Stanniocalcin (STC) immunostain confined to mouse adrenal cortical zones. (Derived from Paciga et al 2005)

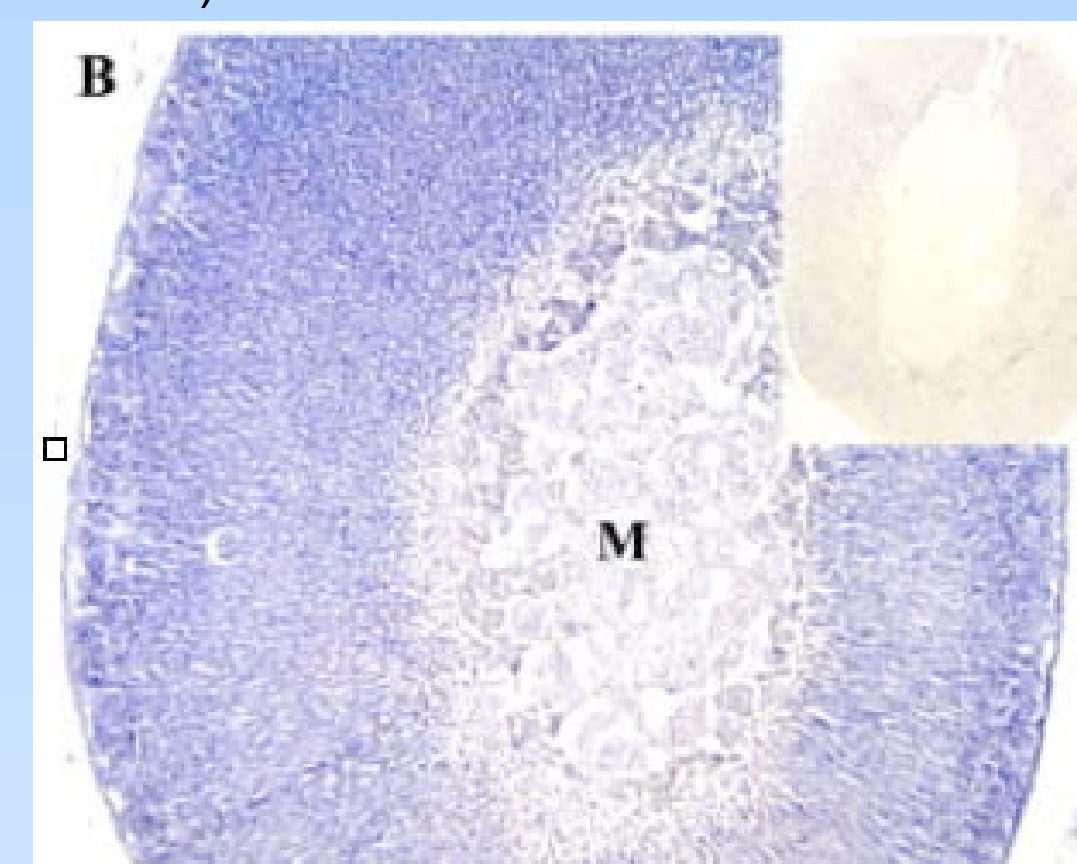


Figure 1B: In situ hybridization showing STC transcription in adrenal cortex, and very little in medulla.

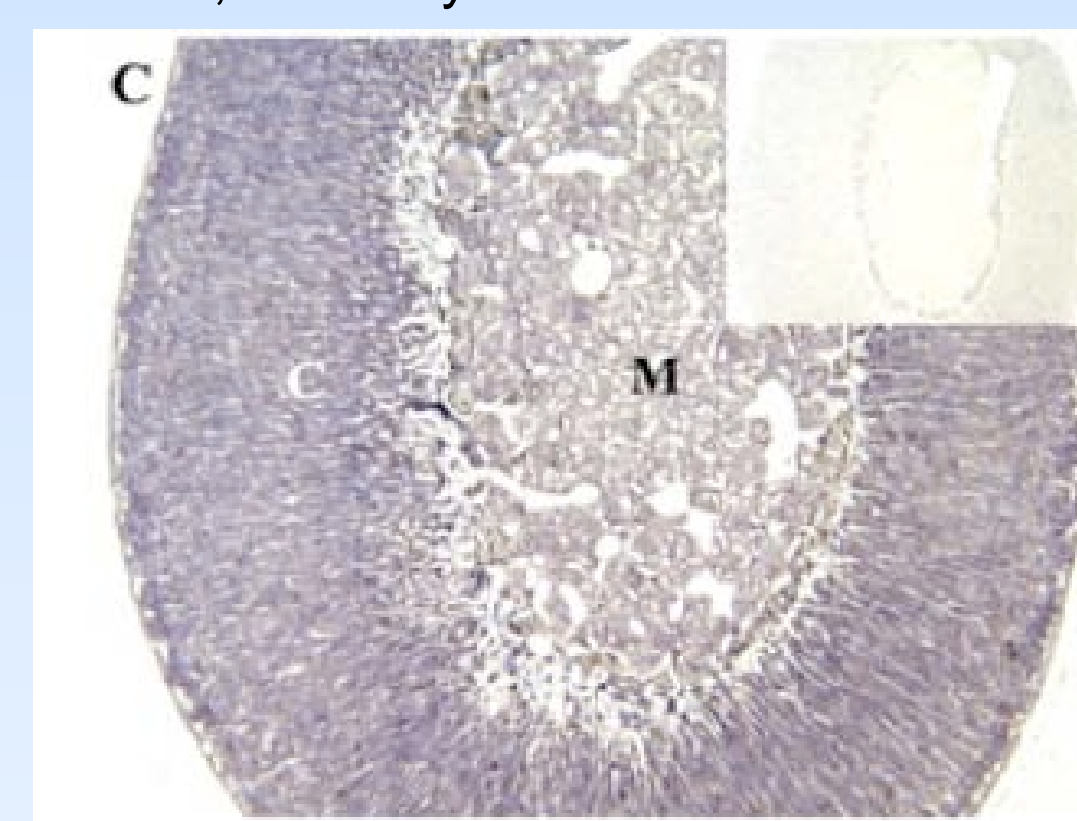


Figure 1C: In situ ligand binding- STC receptors are most prominent in cortex, though medulla shows significant binding activity.

Hypercalcemia	Adrenal Insufficiency
GI •Nausea, vomiting •Abdominal pain •Anorexia, weight loss •Constipation	GI •Nausea, vomiting •Abdominal pain •Anorexia, weight loss •Diarrhea
Neuromuscular •Fatigue, lethargy •Muscle weakness •Behavior changes: Impaired concentration, memory •Confusion, stupor, coma	Neuromuscular •Fatigue, lethargy •Muscular weakness •Behavior changes: anxiety, emotional changes, irritability •Depression
Skeletal •Arthralgias •Bone pain •Osteoporosis	Skeletal •Arthralgias
Cardiovascular •Dehydration •Short QT syndrome	Cardiovascular •Dehydration •Orthostatic hypotension

Figure 2: Clinical characteristics of hypercalcemia and adrenal insufficiency.

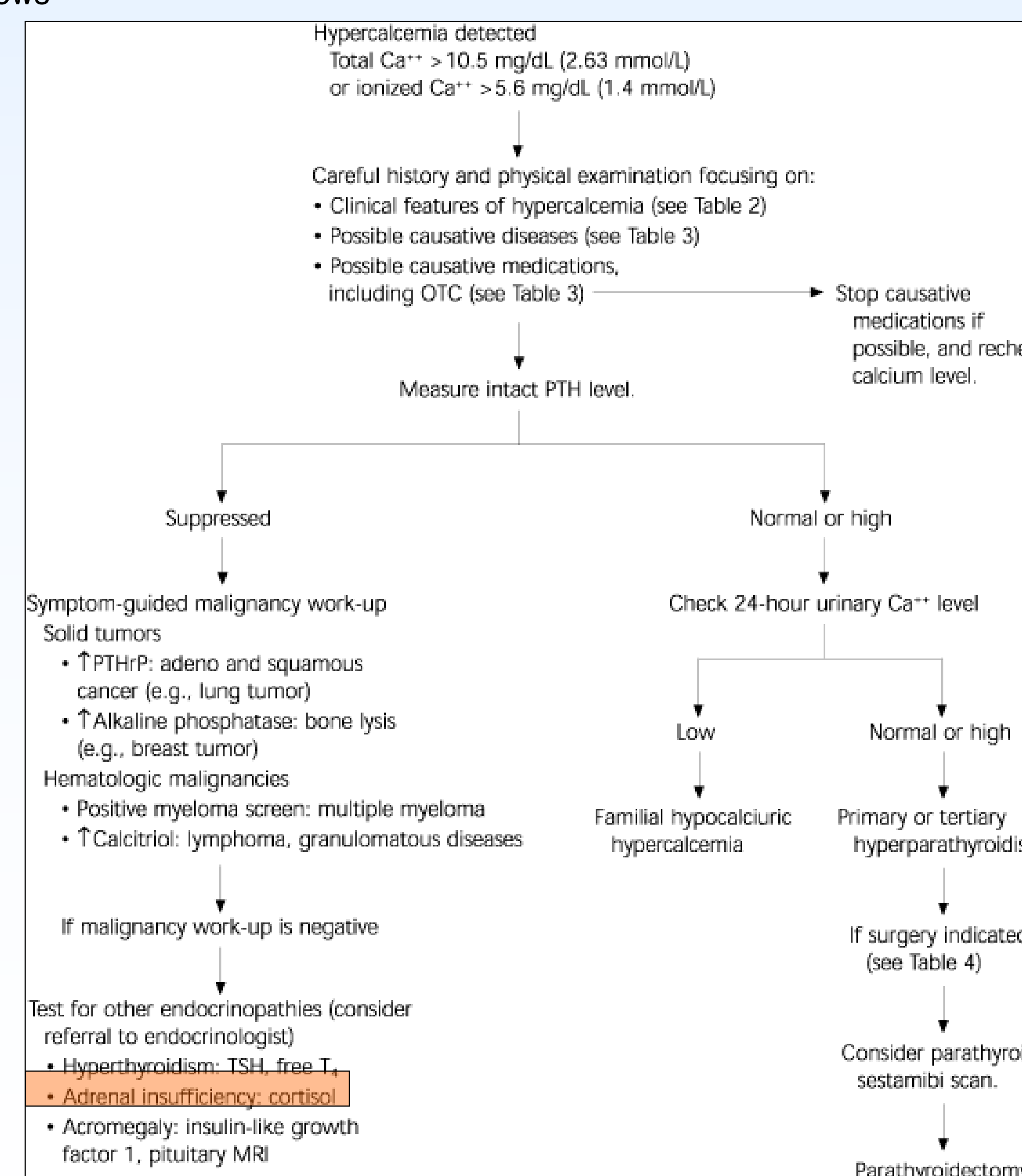


Figure 3: Diagnostic algorithm for hypercalcemia. (Derived from Carroll et al 2003)

DISCUSSION

General

- Uncommon, but well established cause of hypercalcemia
- Prevalence 6% in primary adrenal insufficiency
- Life threatening levels of hypercalcemia uncommon

Mechanisms

- Incompletely understood
- Independent of PTH and Vitamin D effects
- Likely multifactorial
 - Increased calcium resorption from bone via a thyroxine-dependant mechanism has been shown to contribute.
 - Increased proximal tubular sodium reabsorption with associated calcium reabsorption, resulting from decreased GFR from adrenal insufficiency-mediated hypovolemia, is another possible mechanism.
 - Deficiency of **stanniocalcin**, an anti-hypercalcemic hormone discovered in bony fish and produced exclusively in the adrenal cortex, may play a role.
 - Increased gut absorption of calcium does not appear to be a factor.

Clinical Presentation and Diagnosis

•Nonspecific symptoms

- Presentation of hypercalcemia and adrenal insufficiency can be quite similar.
- Adrenal insufficiency should be suspected in all patients with hypercalcemia, particularly with deterioration of symptoms following initiation of thyroid replacement.
- Random serum cortisol useful only in critically ill inpatients, where it should be at a maximum; otherwise, measure **morning serum cortisol**. If **< 3 µg/dL**, patient is adrenally insufficient and no further tests are required.
- For intermediate AM cortisol values, **cosyntropin stimulation test** may be useful. Values greater than 18-20 µg/dL indicate normal HPA axis function.
- Serum ACTH** should be measured to distinguish primary from secondary (central) adrenal insufficiency; normal is 0-50 ng/dL.

Treatment

- Hypercalcemia usually rapidly reversed with aggressive fluid resuscitation and high dose IV glucocorticoids.
- Chronic adrenal insufficiency treated with PO **glucocorticoid replacement**, titrated to physiologic levels.
- Primary adrenal insufficiency requires **mineralocorticoid replacement**, with electrolyte monitoring.
- DHEA replacement** has been shown to increase femoral neck bone mineral density, lean body mass, and overall well-being, while decreasing fatigue

REFERENCES

- Carroll ME, Schade DS. A Practical Approach to Hypercalcemia. *Am. Fam. Phys.* 2003;67:1959-1966.
- Grinspoon SK, Biller BM. Clinical Review 62: Laboratory assessment of adrenal insufficiency. *J Clin Endocrinol Metab.* 1994;79:923-931.
- Gurnell EM et al. Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial. *J Clin Endocrinol Metab.* 2008;93(2):400-409.
- Jacobs TP, Bilezikian JP. Clinical Review: Rare Causes of Hypercalcemia. *J Clin Endocrinol Metab.* 2005;90:6316-6322.
- Katahira M, Yamada T, Kawai M. A Case of Cushing Syndrome with Both Secondary Hypothyroidism and Hypercalcemia Due to Postoperative Adrenal Insufficiency. *Endocr. Jour.* 2004;51:105-113.
- Loeb RF. Chemical changes in the blood in Addison's disease. *Science* 1932;76:420-421.
- Moe SM. Disorders Involving Calcium, Phosphorus, and Magnesium. *Prim. Care* 2008;35:215-234.
- Nair GK, Simmons DL. Adrenal Insufficiency Presenting as Hypercalcemia. *Hosp. Phys.* 2002;January:33-36.
- Pagica M et al. Characterization of big stanniocalcin variants in mammalian adipocytes and adrenocortical cells. *American Journal of Physiology—Endocrinology and Metabolism* 2005;289:197-205.
- Walser M, Robinson BH, Duckett JW. The Hypercalcemia of Adrenal Insufficiency. *Jour. of Clin. Investig.* 1963;42:456-465.