

# Case Study

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A 74 year old woman is seen in the outpatient clinic on a routine follow up visit. Her medical history is significant for type II diabetes mellitus and hypertension, for she has been treated for the past thirty years. She has received several laser photocoagulation treatments for her eyes. She has chronic back pain for which she has been ingesting 4-6 tablets of Ibuprofen daily for the past 4 years. Her medical regimen includes Amlodipine 5 mg, Atenolol 50 mg, Lisinopril 40 mg, Glipizide 5 mg, Cholecalciferol 1000 unit all once daily as well as Furosemide 40 mg twice daily.

On physical examination she is well-appearing and is no apparent distress. Her pulse rate is 66/min, blood pressure is 166/90 and she is afebrile. Neck is supple without lymphadenopathy or thyromegaly. Heart is regular with normal S1/S2 without added sounds and lungs are clear. Abdomen is not tender or distended and she has no organomegaly. Lower extremities revealed trace edema and slight decreased sensation in a glove and stocking pattern.

Her labs showed the following: serum Na 147 mmol/L, K 5.2 mmol/L, Cl 113 mmol/L, HCO<sub>3</sub> is 17 mmol/L, BUN is 98 mg/dL and creatinine is 2.4 mg/dL. When seen at clinic three months ago she had the following chemistry profile: Na 136 mmol/L, K 4.8 mmol/L, Cl 109 mmol/L, HCO<sub>3</sub> 22 mmol/L, BUN 75 mg/dL and creatinine of 2.2 mg/dL. A non-fasting blood sugar is 200 mg/dL. Dipstick urine testing revealed 2+ protein and the urinary sediment was inactive microscopically. A spot urinary protein was 145 mg/dL and creatinine is 66 mg/dL.

1. The most probable underlying cause of renal insufficiency in this patient is:
  - a. Chronic interstitial nephritis secondary to prolonged NSAIDs intake
  - b. Diabetic nephropathy
  - c. Reflux nephropathy
  - d. Ischemic nephropathy secondary to renal artery stenosis
  - e. Rapidly progressive glomerulonephritis

Other labs drawn showed the following: serum albumin is 3.7 g/dL, calcium is 11.3 mg/dL, and phosphorus is 3.6 mg/dL. Her hemoglobin is 12.2 mg/dL, WBC count is 5,000 and platelets are 350,000.

2. The most likely mechanism of elevated serum sodium is:
  - a. An episode of secretory diarrhea
  - b. A central decrease in vasopressin secretion
  - c. A concentrating defect mediated by activation of tubular calcium-sensing receptors
  - d. An osmotic diuresis from uncontrolled diabetes mellitus
  - e. Excessive intake of dietary salt

3. The next step in managing this patient is to:

- a. Send the patient to the ER to receive intravenous fluids and furosemide
- b. Advise on low salt and calcium diet and schedule a follow up visit
- c. Start calcium bicarbonate therapy
- d. Obtain ionized serum calcium, vitamin D and PTH levels
- e. Order a bone densitometry scan

Upon further questioning this patient admits to excessive thirst and nocturia. Ionized calcium was 1.48 mmol/L (normal: 1-1.25 mmol/L (= 4-5 mg/dL), vitamin D-25 level is 17 ng/mL, and intact PTH was 211.3.

4. The most appropriate test at this point is:

- a. Serum and urine protein electrophoresis
- b. Chest x ray
- c. Total body bone scan
- d. Ultrasonographic study of the kidney
- e. SESTAMIBI scan for the neck

5. Appropriate therapeutic interventions for this condition include the following EXCEPT:

- a. Estrogen-progestin supplementation
- b. Vitamin D supplementation
- c. Calcium-sensing receptor agonist
- d. Bilateral neck exploration and parathyroidectomy
- e. Melphalan

**Suggested answers:**

1. **(b)**

*Prolonged NSAIDs intake is often linked with chronic interstitial nephritis but was mainly described with intake of combination analgesics<sup>1,2</sup>, and is unlikely associated with this degree proteinuria. Reflux nephropathy is unlikely in the absence of compatible history. Ischemic nephropathy is possible given cardiovascular risk factors and uncontrolled BP but is less likely than diabetic nephropathy. Supporting clues for the latter include diabetic microvascular complications and subnephrotic proteinuria. RPGN is unlikely given lack of AKI and benign urinary sediment.*

2. **(c)**

*Chronic hypercalcemia leads to a defect in concentrating ability. It has been shown that activation of the normal calcium-sensing receptor by increases in the serum calcium concentration can directly impair concentrating ability by affecting both the loop of Henle and the collecting tubules.<sup>3,4</sup>*

3. **(d)**

*Total serum calcium is high and needs to be confirmed. This is typically done by correcting in reference to the serum albumin (a decrease of albumin by 1 g/dL corrects serum calcium up by 0.8 mg/dL), or even better, obtaining ionized (free) serum calcium level. Intact PTH is important to sort out the diagnosis. A low level would be consistent with neoplastic etiology, granulomatous diseases, thyrotoxicosis, hypervitaminosis A and Paget's disease where PTH would be appropriately suppressed. Alternatively, a high level would suggest primary hyperparathyroidism. Familial hypocalciuric hypercalcemia is also characterized by normal or slightly elevated iPTH with low 24h urinary Ca excretion.<sup>5</sup>*

4. **(e)**

*This intact PTH level is relatively high for this degree of hypercalcemia; therefore a SESTAMIBI scan to look for an adenoma is appropriate. Although this patient has CKD and possible secondary hyperparathyroidism, it is expected that she should be able to appropriately suppress her PTH, unless she has end stage renal disease that might be associated with autonomous PTH release. SPEP, UPEP and skeletal survey are tests for multiple myeloma (MM). Although MM should be suspected in every elderly with hypercalcemia, renal insufficiency and anemia it is unlikely here given the high iPTH. CXR is helpful to look for lung tumors, sarcoidosis or TB which could be associated with hypercalcemia due to increased 1- $\alpha$  hydroxylation of vitamin D, but again this is unlikely in the scenario given the high iPTH.*

5. (e)

*Estrogen has been tried to treat primary hyperparathyroidism at least in females.<sup>6</sup> Subtotal hyperparathyroidectomy is the treatment of choice but occasionally the tumor is difficult to identify, and in 10-15% of cases there is diffuse hyperplasia of all glands. In such cases excellent results have been achieved by using the calcium sensing receptor agonist Cinacalcet which allows normalization of serum calcium and PTH.<sup>7</sup> If documented, vitamin D deficiency (defined as  $\leq 20$  ng/mL [50 nmol/L]) should be treated prior to treating primary hyperparathyroidism.<sup>8</sup> Melphalan is the treatment of multiple myeloma which is unlikely in this scenario.*

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<sup>1</sup> R John and A M Herzenberg. Renal toxicity of therapeutic drugs. J Clin Pathol 2009 62: 505-515

<sup>2</sup> De Broe ME et al. Analgesic nephropathy. Nephrol Dial Transplant. 1996;11(12):2407-8.

<sup>3</sup> Sands JM et al. Apical extracellular calcium/polyvalent cation-sensing receptor regulates vasopressin-elicited water permeability in rat kidney inner medullary collecting duct. J Clin Invest 1997;15;99(6):1399-405.

<sup>4</sup> Hebert, SC. Extracellular calcium-sensing receptor: Implications for calcium and magnesium handling in the kidney. Kidney Int 1996; 50:2129.

<sup>5</sup> El-Hajj Fuleihan, G et al. In: The Parathyroids: Basic and Clinical Concepts, Bilezikian, JP, Marcus, R, Levine, MA (Eds), Academic Press, San Diego 2001. p. 607.

<sup>6</sup> Marcus, R et al. Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. Ann Intern Med 1984; 100:633.

<sup>7</sup> Marcocci C et al. Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab. 2009;94(8):2766-72..

<sup>8</sup> Eastell R et al. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab. 2009;94(2):340-50.