

70-Year-Old Man With Dizziness and Nausea



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A 70-year-old man presented to the emergency department for intermittent dizziness, nausea, and weakness over the past 3 months. His symptoms had been worsening over the past week, and he was vomiting after any oral intake for the past 2 days. Review of systems was notable for fatigue, confusion, forgetfulness, 9-lb weight loss, and worsening chronic dry cough. He denied fever, chills, headache, shortness of breath, chest pain, abdominal pain, constipation, kidney stones, urinary frequency, or pain with urination.

His medical comorbidities included atrial fibrillation, hypertension on valsartan-hydrochlorothiazide, type 2 diabetes mellitus, and severe aortic stenosis status after recent transcatheter aortic valve replacement. Approximately 4 months before presentation, he underwent computed tomography coronary angiogram as part of evaluation for his transcatheter aortic valve replacement, which incidentally revealed bilateral solid pulmonary nodules, mediastinal lymphadenopathy, and right greater than left hilar lymphadenopathy. He subsequently had a positron emission tomography scan revealing minimal uptake in the pulmonary nodules and marked fluorodeoxyglucose activity in the mediastinal and hilar lymph nodes.

On presentation, he was hypertensive at 158/91 mm Hg with a heart rate of 66 beats/min. Physical examination revealed a well-appearing man with dry mucous membranes; no cervical, submandibular, or supraclavicular lymphadenopathy; normal jugular venous pressure; regular heart rate and rhythm; clear lung fields; and a nontender abdomen. Laboratory results revealed the following (reference ranges are provided parenthetically): hemoglobin, 13.6 g/dL

(13.2 to 16.6 g/dL); white blood cell count, $7.5 \times 10^9/L$ ($(3.4$ to $9.6) \times 10^9/L$); creatinine, 3.61 mg/dL (0.74 to 1.35 mg/dL), which increased from a baseline of 1.04 mg/dL; sodium, 138 mmol/L (135 to 145 mmol/L); potassium, 4.0 mmol/L (3.6 to 5.2 mmol/L); total calcium, 14.6 mg/dL (8.8 to 10.2 mg/dL); albumin, 3.7 g/dL (3.5 to 5.0 g/dL); total protein, 6.2 g/dL (6.3 to 7.9 g/dL); magnesium, 1.8 mg/dL (1.7 to 2.3 mg/dL); C-reactive protein, 12.1 mg/L (≤ 8.0 mg/L); and alkaline phosphatase, 116 U/L (40 to 129 U/L). His serum calcium level was rechecked and found to be 13.4 mg/dL.

1. Which one of the following is the *best* initial test to obtain in the work-up of this patient's hypercalcemia?

- Ionized calcium
- Parathyroid hormone (PTH)
- 24-Hour urine calcium
- Parathyroid-related peptide (PTHrP)
- 25-Hydroxyvitamin D

After performing a history and physical examination from a patient presenting with hypercalcemia, the serum calcium level should be rechecked to confirm hypercalcemia. About half of calcium in the blood is bound to proteins or complexed to anions, whereas the other half is ionized and unbound. Ionized calcium is the physiologically active form of calcium. Total serum calcium concentrations may not accurately reflect levels of ionized calcium if there are derangements in albumin levels.¹ Several formulas can be used to calculate the corrected calcium level. An alternative is to collect an ionized calcium level, which accurately reflects physiological calcium levels in the setting of serum protein abnormalities. This patient's albumin level is 3.7 g/dL and

See end of article for correct answers to questions.

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within the normal range, so an ionized calcium level would not be the next best test to obtain.

The best next step in evaluating hypercalcemia is to obtain a PTH level. Conditions associated with hypercalcemia can be categorized into disease processes with an inappropriately elevated or normal PTH level (PTH-dependent causes) and those with PTH levels that are appropriately suppressed (PTH-independent causes). Parathyroid hormone–dependent causes include primary hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH). Parathyroid hormone–independent causes include vitamin D intoxication, vitamin A intoxication, thyrotoxicosis, immobilization, milk-alkali syndrome, granulomatous disease such as sarcoidosis, lymphoma, multiple myeloma, and other malignant neoplasms.²

In patients with PTH-dependent hypercalcemia, a 24-hour urinary calcium can help distinguish whether they have primary hyperparathyroidism or FHH. Urinary calcium excretion is low in patients with FHH (typically below 200 mg/d). A urine calcium/creatinine ratio of less than 0.02 is suggestive of FHH, whereas a high urine calcium/creatinine ratio suggests primary hyperparathyroidism.²

This patient has unexplained weight loss, fatigue, worsening dry cough, and incidentally found bilateral pulmonary nodules, making malignancy a possibility. There are 4 mechanisms for hypercalcemia in malignancy: direct overproduction of PTHrP by tumor cells; excess synthesis of 1,25-dihydroxyvitamin D, leading to increased intestinal calcium absorption; bone breakdown from multiple myeloma, metastases, or local cytokines release; and excess PTH secretion by tumor cells.² A PTH level should be checked to confirm PTH-independent cause of hypercalcemia before obtaining a PTHrP level.

Patients with vitamin D intoxication can have hypercalcemia from increased enteric absorption and bone resorption of calcium. In vitamin D intoxication, 25-hydroxyvitamin D levels are typically higher

than 150 ng/mL and circulating levels of 1,25-dihydroxyvitamin D are normal or near normal.³

This patient's PTH level was less than 6 pg/mL (15-65 pg/mL). Because his PTH level was low, further laboratory work-up included the following: PTHrP, 1.1 pmol/L (≤ 4.2 pmol/L); thyroid-stimulating hormone, 2.08 mIU/L (0.27 to 4.20 mIU/L); 25-hydroxyvitamin D, 66 ng/mL (25 to 50 ng/mL in healthy populations); and 1-25-dihydroxyvitamin D, 67 pg/mL (18 to 64 pg/mL). Serum protein electrophoresis revealed a 0.84 albumin/globulin ratio and no apparent monoclonal protein. Urine protein electrophoresis revealed a total 24-hour protein of 700 mg/24 h (< 229 mg/24 h) and no apparent monoclonal spike.

2. Given this patient's clinical presentation and laboratory work-up so far, which one of the following is the most likely primary diagnosis?

- a. Primary hyperparathyroidism
- b. Humoral hypercalcemia of malignancy
- c. Sarcoidosis
- d. Multiple myeloma
- e. Medication toxicity

Because this patient's PTH level was low at less than 6 pg/mL, primary hyperparathyroidism is not the most likely diagnosis.

Humoral hypercalcemia of malignancy is the most common cause of hypercalcemia of malignancy and is characterized by excessive secretion of PTHrP.¹ It is a PTH-independent cause of hypercalcemia and should be suspected in patients with malignancy without skeletal metastases. This patient's nonspecific symptoms and imaging findings of bilateral pulmonary nodules and lymphadenopathy raise suspicion for malignancy; however, his normal PTHrP points against the diagnosis of humoral hypercalcemia of malignancy.

Sarcoidosis causes PTH-independent hypercalcemia through enhanced conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by macrophages. This patient's mediastinal lymphadenopathy on chest computed tomography, accompanied

by a low PTHrP level and an elevated 1,25-dihydroxyvitamin D level, supports sarcoidosis as the most likely diagnosis of the answer choices. A non-PTHrP-mediated cause of malignancy would also remain in the differential diagnosis.

Multiple myeloma should be in the differential given this patient's hypercalcemia and renal dysfunction. Hypercalcemia in multiple myeloma is secondary to widespread tumor-induced bone destruction from increased osteoclast activity.² This patient had a normal gamma gap of 2.5 and serum protein electrophoresis revealed no apparent monoclonal protein. These laboratory findings, as well as lack of bone pain and anemia, make multiple myeloma less likely.

This patient is taking hydrochlorothiazide. Hypercalcemia is a well-known adverse effect of this medication. Reaching serum calcium levels greater than 11.5 mg/dL as a medication adverse effect alone is rare. Many patients with thiazide-associated hypercalcemia have underlying primary hyperparathyroidism.⁴ Although hydrochlorothiazide use is likely exacerbating his hypercalcemia, it is unlikely to be the primary diagnosis.

Treatment of his hypercalcemia and additional work-up for sarcoid vs malignancy were initiated. His hydrochlorothiazide was discontinued.

3. Which one of the following treatments is the most appropriate next step in management?

- Intravenous normal saline
- Cinacalcet
- Intravenous zoledronic acid
- Denosumab
- Subcutaneous calcitonin

Management of hypercalcemia depends on the serum calcium level and the presence of clinical symptoms. Asymptomatic patients and those with mild hypercalcemia (<12.0 mg/dL) generally do not require acute treatment. Symptomatic patients with calcium levels between 12.0 and 14.0 mg/dL require acute treatment, and patients with

serum calcium level greater than 14.0 to 15.0 mg/dL require treatment regardless of symptoms as they are at risk for arrhythmias, coma, and death.⁵

Patients with hypercalcemia are often profoundly volume depleted secondary to nausea, vomiting, and polyuria from calcium-induced diuresis. They should immediately undergo fluid resuscitation.² Loop diuretics can be used to offset fluid overload from volume expansion and are sometimes used to augment calciuresis despite little evidence to support this practice.¹

Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor on the parathyroid gland, thereby lowering PTH and subsequently lowering serum calcium levels. There is evidence supporting its use in the treatment of hypercalcemia secondary to renal failure, parathyroid cancer, and primary hyperparathyroidism.¹ This is not the best next treatment.

Zoledronic acid is a bisphosphonate, which reduces bone resorption through the inhibition of the recruitment, activity, and survival of osteoclasts. The maximum effects of bisphosphonates are evident 2 to 4 days after administration. Bisphosphonates should be used with caution in those with renal impairment.^{1,2} This patient has poor renal function, so zoledronic acid should be avoided. Additionally, because it has a longer time to action, it is not the next best step in the acute management of his hypercalcemia.

Denosumab is a fully human monoclonal antibody that binds to the receptor activator of nuclear factor kappa beta ligand and inhibits the activation and function of osteoclasts. Denosumab is not cleared renally and is reserved for the treatment of hypercalcemia in patients who cannot tolerate bisphosphonates or were nonresponsive to bisphosphonates.¹

Subcutaneous calcitonin reduces calcium by increasing renal calcium excretion and by decreasing bone resorption and begins working within several hours. It has very few

adverse effects, but patients can develop tachyphylaxis after 24 to 48 hours. Calcitonin would be a reasonable medication to administer after initiating intravenous fluids.¹

This patient received 400 U of subcutaneous calcitonin in addition to 4 L of intravenous fluids and had improvement in his calcium level to 11.2 mg/dL. He had improvement in his nausea and confusion. He underwent bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration of his mediastinal and hilar lymph nodes. Biopsies were negative for malignancy and revealed granulomatous inflammation with negative acid-fast bacilli and Gomori methenamine silver stains.

4. Which one of the following criteria is most likely needed to confirm this patient's diagnosis?

- Presence of noncaseating granuloma on tissue biopsy alone
- Compatible clinical presentation and radiographic evidence of disease
- Presence of noncaseating granuloma on tissue biopsy plus elevated serum angiotensin-converting enzyme level
- Presence of noncaseating granuloma on tissue biopsy, compatible clinical presentation, and exclusion of other causes of granulomatous inflammation
- Presence of noncaseating granuloma on tissue biopsy, compatible clinical presentation, exclusion of other causes of granulomatous inflammation, radiographic evidence of disease, and abnormal pulmonary function tests

This patient underwent lymph node biopsies, which were negative for malignancy. Therefore, sarcoidosis was the leading diagnosis. The presence of noncaseating granuloma on histopathology is required for the diagnosis of sarcoidosis. If there is suspicion for disease involvement in superficial areas such as the skin, superficial lymph node, or lacrimal gland, these are the preferred biopsy sites. If these lesions are not present, intrathoracic lymph nodes or lung parenchyma

are the next preferred biopsy sites.⁶ Additional criterion must be met in addition to biopsy findings to make the diagnosis of sarcoidosis.

Radiographic features of pulmonary sarcoidosis vary by stage (I-IV) and include bilateral hilar lymphadenopathy, parenchymal infiltration, and advanced fibrosis, depending on stage. The diagnosis of sarcoidosis cannot be definitively made on the basis of clinical and radiological findings alone.⁶

Elevated serum angiotensin-converting enzyme levels were previously thought to be indicative of disease activity in sarcoidosis. Studies have reported that it is a nonspecific and nonsensitive test, and it has limited utility in the diagnosis or measurement of disease activity.⁷ Angiotensin-converting enzyme levels are not included as part of the diagnostic criteria for sarcoidosis.

The diagnosis of sarcoidosis relies on all the following 3 criteria: presence of noncaseating granuloma on histopathological examination, a compatible clinical presentation, and exclusion of other causes of granulomatous inflammation.⁸ Therefore, option "d" is the best answer. The differential for granulomatous disorders is broad, and the tests needed for diagnosis are driven by patient history, physical examination, radiographic features, and risk factors.⁸

In patients with pulmonary sarcoidosis, pulmonary function tests and chest radiography are recommended to provide a baseline of disease involvement and are used to monitor disease progression. They are not required for the initial diagnosis of sarcoidosis.

The results of additional testing including fungal serologies for histoplasmosis and blastomycosis were negative. Pulmonary function testing was suggestive of mildly restrictive lung disease (total lung capacity, 80% predicted) with normal spirometry and diffusing capacity of lung for carbon monoxide (119% predicted) thought to be secondary to obesity. Outpatient follow-up with pulmonology was arranged.

After his hospitalization, he continued to have renal dysfunction, and renal biopsy revealed granulomatous tubulointerstitial nephritis, consistent with renal sarcoidosis.

5. Which one of the following treatments is most appropriate to initiate for management of this patient's disease?

- a. No systemic treatment is indicated
- b. Prednisone
- c. Methotrexate
- d. Azathioprine
- e. Ketoconazole

Pulmonary sarcoidosis often undergoes spontaneous regression without causing permanent damage. Systemic therapy is recommended for patients with progressive symptomatic disease, persistent pulmonary infiltration, and progressive decline of lung function.⁹ Because this patient had hypercalcemia and a symptomatic manifestation of sarcoidosis, treatment is indicated.⁶

Glucocorticoids are the mainstay of therapy in those who require treatment for sarcoidosis. A recommended initial dose of prednisone is 20 to 40 mg/d or its equivalent for 1 to 3 months before a gradual taper if symptoms, radiographic changes, and pulmonary function tests are improved.⁶ This is the best initial treatment for this patient.

Glucocorticoid-sparing agents and biologics are reserved for refractory cases of sarcoidosis. Methotrexate is an effective agent in chronic sarcoidosis. It is typically given as 10 to 25 mg/wk orally or intramuscularly, though doses greater than 15 mg are generally not used, as the adverse effects, including nausea and vomiting, outweigh the benefits at higher doses.¹⁰ Its maximum effect is not evident for 2 to 3 months after initiating therapy.⁶ It must be used with caution in patients with renal disease.

Azathioprine can be used as a steroid-sparing agent in the treatment of sarcoidosis. There is a small body of evidence supporting its use.¹¹ The maintenance dose is 2 mg/kg per day.

Ketoconazole 600 to 800 mg/d may be effective in treating hypercalcemia in

sarcoidosis, as it inhibits cytochrome P450 enzymes, including 1-hydroxylase, which will subsequently lower 1,25-hydroxyvitamin D and calcium levels.¹¹ Hepatic toxicity is an adverse effect of this treatment.

He was initiated on prednisone 20 mg/d with addition of an insulin regimen upon discharge because of steroid-induced hyperglycemia while hospitalized.

DISCUSSION

Sarcoidosis is a multisystem disease of granulomatous inflammation that can affect virtually any organ, though most commonly involves the lungs and intrathoracic lymph nodes. It has a heterogeneous presentation, making it a diagnostic challenge for many clinicians.^{6,8} Disease manifestations are often more severe in Black patients.⁸ Deficiency of 25-hydroxyvitamin D is nearly universal in patients with sarcoidosis, although this patient did not have this finding.¹² Although hypercalcemia is well-studied in sarcoidosis, it is a rare presenting symptom.¹ Hypercalcemia is more common in Caucasian men older than 40 years.¹²

Clinical symptoms of hypercalcemia are usually evident at serum calcium levels greater than 12.0 mg/dL and include nonspecific gastrointestinal symptoms; bone-related complications such as bone pain, osteoporosis, and pathologic fractures; genitourinary symptoms including renal stones, polyuria, and polydipsia; and neuropsychiatric manifestations including lethargy, confusion, and memory loss. Other clinical features include muscle weakness, arrhythmias, and electrocardiographic changes including prolonged QRS and PR intervals, T-wave inversion, and bradycardia.⁵

The most common causes of radiographically detectable mediastinal lymphadenopathy are sarcoidosis, lymphoma, metastatic tumor, and granulomatous infections. For patients with asymptomatic bilateral hilar lymphadenopathy, the American Thoracic Society makes no recommendation for or against obtaining a lymph node sample. If a

lymph node sample is not obtained, the patient must have close clinical follow-up. For patients with suspected sarcoidosis and mediastinal or hilar lymphadenopathy who need tissue biopsy to help confirm the diagnosis, an endobronchial ultrasound-guided lymph node sample is preferred over mediastinoscopy.⁸ The diagnosis of sarcoidosis requires the exclusion of other causes of granulomatous inflammation. The differential for granulomatous inflammation can generally be categorized into infectious and noninfectious causes. Infectious causes include tuberculosis, atypical mycobacterial infections, and fungal infections from *Histoplasma*, *Cryptococcus*, and *Coccidioides*. Noninfectious etiologies include bronchocentric granulomatosis, inflammatory bowel disease, hypersensitivity pneumonitis, berylliosis, and granulomatous with polyangiitis. Work-up for these etiologies should be guided by patient risk factors and clinical presentation.⁸

Steroids treat hypercalcemia in sarcoidosis by inhibiting macrophage 1-hydroxylase activity. There is no evidence-based optimal dose and duration of therapy. Tapers typically reduce the daily dose by 5 to 10 mg every 1 to 3 months. Total glucocorticoid therapy should last approximately 1 year. Improvements in calcium level are usually evident within the first week of treatment.⁶ Long-term glucocorticoid therapy has adverse effects on mood, bone metabolism, blood glucose levels, and weight. Relapse occurs in as many as 30% of patients after discontinuing steroids.⁶

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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REFERENCES

1. Maier JD, Levine SN. Hypercalcemia in the intensive care unit: a review of pathophysiology, diagnosis, and modern therapy. *J Intensive Care Med*. 2015;30(5):235-252.
2. Renaghan AD, Rosner MH. Hypercalcemia: etiology and management. *Nephrol Dial Transplant*. 2018;33(4):549-551.
3. Marciniowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Pludowski P, Jones G. Vitamin D toxicity—a clinical perspective. *Front Endocrinol (Lausanne)*. 2018;9:550.
4. Griebeler ML, Kearns AE, Ryu E, et al. Thiazide-associated hypercalcemia: incidence and association with primary hyperparathyroidism over two decades. *J Clin Endocrinol Metab*. 2016;101(3):1166-1173.
5. Sadiq NM, Naganathan S, Badireddy M. Hypercalcemia. In: StatPearls [Internet]. StatPearls Publishing; 2021.
6. Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis, and treatment of sarcoidosis. *Mayo Clin Proc Innov Qual Outcomes*. 2019;3(3):358-375.
7. Ungprasert P, Cammona EM, Crowson CS, Matteson EL. Diagnostic utility of angiotensin-converting enzyme in sarcoidosis: a population-based study. *Lung*. 2016;194(1):91-95.
8. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;201(8):e26-e51.
9. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis: American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999;16(2):149-173.
10. Cremers JP, Drent M, Bast A, et al. Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide. *Curr Opin Pulm Med*. 2013;19(5):545-561.
11. Hilderson I, Van Laecke S, Wauters A, Donck J. Treatment of renal sarcoidosis: is there a guideline? Overview of the different treatment options. *Nephrol Dial Transplant*. 2014;29(10):1841-1847.
12. Burke RR, Rybicki BA, Rao DS. Calcium and vitamin D in sarcoidosis: how to assess and manage. *Semin Respir Crit Care Med*. 2010;31(4):474-484.

CORRECT ANSWERS: 1. b. 2. c. 3. a. 4. d. 5. b