

You're the Flight Surgeon

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You are the primary flight surgeon in charge of an Air Force C-130 squadron in northern Europe. You have enjoyed your first year at this assignment and have avoided frostbite thus far. You have been caring for an experienced 41-yr-old loadmaster for the last 8 mo on a regular basis.

You have seen him for a variety of seemingly unrelated complaints. He has seen you off and on for difficulty sleeping and fatigue, decreased concentration, low back pain, and sexual dysfunction. He has been coping well, but he is now concerned about “not feeling like himself” and his condition is starting to stress him out. He denies any feelings of, or personal or family history of, depression. He reports enjoying his job and having a good family life. None of your workup thus far has identified any chronic condition, and his intermittent symptoms of low back pain and sexual dysfunction have moderately improved with medication.

His family history includes a mother with hypertension, a father with type II diabetes, and a sister with hypothyroidism. He has never smoked, drinks 1–2 beers per week and 5–6 caffeinated beverages per week, and denies illicit drug use. He has good sleep, exercise, and diet routines. He takes ibuprofen occasionally for his back pain 4 times per week, sildenafil 1–2 times per week, and a multivitamin daily. His surgical history includes a tonsillectomy as a child and a bunionectomy 3 yr ago.

His physical exam reveals his vital signs are within normal limits, except for his body mass index of 28. He appears tired and he has dry skin. His remaining exam is benign.

You had previously considered sleep apnea and ordered a polysomnography, which was negative. His labs, including complete blood count, comprehensive metabolic panel, and thyroid-stimulating hormone, were all within normal limits, with the exception of his calcium, which was $10.5 \text{ mg} \cdot \text{dL}^{-1}$ ($8.9\text{--}10.2 \text{ mg} \cdot \text{dL}^{-1}$). Grateful for something to work with, you start considering how to proceed.

1. What should you do next?

- Order repeat calcium corrected for albumin and parathyroid labs.
- Order imaging of his neck.
- Start bisphosphonate therapy.
- Reassure him that the condition is transient and continue symptomatic care.

ANSWER/DISCUSSION

1. A. It is important to repeat the calcium labs to confirm the hypercalcemia.¹⁰ Total calcium levels should be obtained and any historical labs compared.^{4,10} Correcting calcium levels for albumin, especially in a particularly ill or malnourished patient, can better evaluate ionized calcium levels, which represent the free calcium that is physiologically active.^{4,8} Fortunately, your patient presents as relatively healthy and your lab reports ionized calcium levels, so this compensation is not essential. A parathyroid assay (PTH) should also be ordered to differentiate between parathyroid-mediated and nonparathyroid-mediated hypercalcemia.⁴

You order his calcium level and PTH. The results of his calcium lab return quickly and show his calcium is still elevated at $11 \text{ mg} \cdot \text{dL}^{-1}$. However, his PTH is still pending. When you call to inform him of his results, you learn that there has been no change in his condition and that he is anxious to know what is causing his elevated labs and how you are going to help him.

2. What is the least likely cause of hypercalcemia?

- Primary hyperparathyroidism (PHPT).
- Hypercalcemia of malignancy.
- Familial hypocalciuric hypercalcemia (FHH).
- Multiple endocrine neoplasia type 2 (MEN2).

ANSWER/DISCUSSION

2. C. FHH is an autosomal dominant disorder occurring in about 1 in 78,000 individuals and is the least common cause among the choices.⁷ MEN2 is also a genetic disorder, affecting an estimated 1 in 35,000 people, and leads to primary tumors in the thyroid, parathyroid, and adrenal glands.¹⁶ These two causes are associated with less than 10% of cases involving hypercalcemia.⁸ On the other hand, PHPT and malignancy account for approximately 90% of hypercalcemic patients.⁸

Clinical history, physical exam, and laboratory studies will help you break down these different diagnoses. In addition to the rarity of FHH and MEN2, your loadmaster has no significant family history, making

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these less likely etiologies. The classic presentation for PHPT is asymptomatic mild hypercalcemia discovered incidentally on routine labs.² However, atypical symptomatic individuals may present with vague to frank symptoms secondary to their disrupted calcium homeostasis.² In contrast, malignancy will often present with higher calcium levels than PHPT and clinically significant changes on the physical exam associated with the malignancy by the time it causes hypercalcemia.² These higher levels of hypercalcemia seen in malignancy will often manifest across multiple organ systems. Symptoms may include the following: renal (polyuria, polydipsia, nephrolithiasis, acute and chronic renal insufficiency); gastrointestinal (anorexia, nausea, vomiting, constipation, pancreatitis, peptic ulcer disease); musculoskeletal (muscle weakness, bone pain, osteopenia/osteoporosis); neurological (decreased concentration, confusion, fatigue); or cardiovascular (bradycardia, hypertension).¹²

Unfortunately, hypercalcemia of malignancy is a late finding and often associated with disseminated disease and a poor prognosis. Of individuals with hypercalcemia of malignancy, 80% will die within 1 yr.¹¹ Hypercalcemia of malignancy is most commonly seen in lung cancer, multiple myeloma, and renal cell carcinoma.⁶ It can occur regardless of bone metastasis through a dysregulation of osteoblast and osteoclast activity, leading to bone resorption.^{6,11}

An evaluation of PTH levels provides additional clarity to the case. Elevated PTH is found in 80–90% of PHPT, which would differentiate PHPT from other causes that typically have normal PTH levels.¹³ The exception is a markedly elevated PTH, which would suggest a parathyroid malignancy.¹³ You may also consider ordering 24-h urine calcium and creatinine levels in cases with borderline labs. A urine calcium to creatinine ratio > 0.02 will effectively rule out FHH over PHPT.¹⁰

Your patient's PTH finally returns at 82 pg · mL⁻¹ (10–65 pg · mL⁻¹). You inform him that his labs are consistent with PHPT, his prognosis is good, and you have a plan.

Your loadmaster has no significant family history and a normal physical exam with the exception of his subjective complaints, mildly elevated calcium levels, and elevated PTH. This makes the diagnosis of PHPT most likely, and you breathe a sigh of relief.

3. How should you manage PHPT?

- A. Begin bisphosphonate therapy.
- B. Send him to Interventional Radiology for fine needle aspiration (FNA) of the parathyroid.
- C. Obtain a surgical consult from Otorhinolaryngology, General Surgery, or Endocrine Surgeon.
- D. Order genetic tests, looking for the *RET* proto-oncogene on chromosome 10.

ANSWER/DISCUSSION

3. C. Parathyroidectomy is the only definitive treatment for PHPT.¹³ However, if the patient does not want surgery, or is not a good candidate, some medical management, such as bisphosphonate or hormone therapy, is available to minimize sequella.¹ Fine needle aspiration is not an appropriate treatment option. Genetic tests are also incorrect; the *RET* proto-oncogene on chromosome 10 is associated with MEN2 and

used in diagnosis.¹⁶ Your loadmaster is young and otherwise healthy. With his current diagnosis and symptoms, he is an excellent candidate for surgery.

He is excited to know that he is not going crazy or just getting old, but he is hesitant about surgery. After explaining to him how his untreated condition and current symptoms increase his risk to the mission when performing flight duties, he is more amenable to surgical treatment.

4. What additional concerns should you express to the loadmaster about chronic untreated hypercalcemia?

- A. Related genetic disorders.
- B. Patchy hair loss.
- C. Increased risk for renal stones.
- D. Seizure risks.

ANSWER/DISCUSSION

4. C. Elevated blood calcium levels can lead to hypercalciuria. This increased concentration of calcium in the kidneys can lead to the formation of calcium-related nephrolithiasis.³

You explain to him about his risk for renal stones and how it could lead to sudden incapacitation in the aircraft. He then recalls the experience of a younger airmen in his squadron who had renal stones and begged for the pain to go away. He then asks how soon he can see the surgeon. You consult your otolaryngologist, who sees the patient, reviews his case, and recommends surgery. Presurgery imaging shows a 5-mm mass on the left inferior parathyroid gland. The member consents to surgery and has a successful excision of the mass. The pathology from his surgery is consistent with a parathyroid adenoma, a benign tumor that caused his PHPT.

He is monitored postoperatively and his labs quickly return to normal and remain stable at 2 wk. He reports a significant improvement in the way he feels, and thanks you profusely.

This same loadmaster presents to the clinic 3 wk postop to ask you when he can start flying again. His symptoms have completely resolved, he has stopped taking any medication, and he has been cleared by the otolaryngologist. He says he hasn't felt this good since he was in his 20s and wants to get back to work.

5. When should you return him to flight duty?

- A. Immediately! He feels great.
- B. After waiver approval.
- C. After 3-mo follow-up.
- D. It depends.

ANSWER/DISCUSSION

5. D. The decision to medically return him to flying duties depends on from which organization you are seeking medical clearance. The Army, Navy, and Air Force waiver guides do not specifically address hypercalcemia or hyperparathyroidism as waiver topics. However, they do note that a workup for hypercalcemia should be done to evaluate for hyperparathyroidism and malignancy, including MEN2, as

differential diagnoses under several waiver topics.^{9,14,15} They also note that hyperparathyroidism and the related hypercalcemia can predispose the aircrew member to renal stones, which may require a waiver.^{9,14,15} The type and severity of the presenting symptoms, as well as any functional impairment, may also require waiver consideration. The Federal Aviation Administration is more specific. They require clinical notes, current medication use and side effects, as well as current calcium and phosphorus levels for consideration. However, if the individual is postsurgery, stable, and without sequelae, then an aviation medical examiner can issue the medical certificate.⁵

Since this loadmaster is in the Air Force and has had a complete recovery without complications, you return him to flying status and excitedly join him on his first flight back. While cruising in low level flight, you get harnessed in to enjoy the view out the open ramp door of your C-130 and remember why you love this job.

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