You're the Flight Surgeon

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You are the new flight surgeon at a U.S. Air Force tanker squadron when a 31-yr-old male boom operator with 1200 h comes to you complaining of increasing breast tissue. He states this is uncomfortable when he is in any position that puts pressure on the area. This is especially noticeable when lying in the prone position during his duties as a boom operator.

To determine the cause of breast growth and tenderness, you perform a thorough history and physical. Your boom operator reports a normal puberty and denies any noticeable breast growth before the last several years. He felt like the right breast was getting larger over the last 2 yr with increasing discomfort and sensitivity. He denied nipple discharge, skin changes, and galactorrhea. He does admit to lower libido in the past year or so, but denies impotence. He shaves daily, does not feel fatigued, and denies previous testicular injury or pain. There is no history of headaches or diplopia, but he may have experienced blurry vision in the past.

Social history reveals he is married with no children and is a lifetime nonsmoker who drinks two to three beers each weekend. This patient has a high level of physical fitness and actively trains in mixed martial arts. As a part of his fitness regimen, he uses whey protein powder daily but takes no other supplements, herbal preparations, or over-the-counter or prescription medications. His past medical history is significant only for remote fractures, which have healed without sequela.

Physical exam reveals a healthy-appearing man with a body mass index of 23 and normal vitals. The only remarkable findings on exam are Tanner Stage 2 breast development, with a 2-cm by 2-cm rubbery mass felt concentric to the right areola, with a similar 1.5-cm by 1.5-cm finding on the left. The exam is negative for nipple discharge and breast tenderness. Testicular volume is measured as 20 mL by orchidometer. Examination of the thyroid, abdomen, and testicles is normal, with no overt findings of hypogonadism, liver disease, or hypothyroidism. Fundoscopy is normal, and visual acuity and in-office visual fields show no decrement.

1. Given the above history and exam findings, what is the most likely diagnosis?

A. Gynecomastia.
B. Pseudogynecomastia.
C. Breast carcinoma.
D. Normal finding.

ANSWER/DISCUSSION

1. A. Gynecomastia is defined as a benign proliferation of ductal epithelium in males, which is due to a relative regional increase of free estrogen to androgen. On exam, a symmetrically shaped, rubbery to firm mass of tissue at least 0.5 cm in diameter may be palpated directly below the areola. It usually affects both breasts, but may present asymmetrically, or as a unilateral enlargement.[13] The mass is often mobile and may be associated with pain and tenderness if the growth is recent in onset. In contrast, pseudogynecomastia may be seen in obese males and consists of increased adipose tissue within the breast tissue without glandular proliferation.[2] Features concerning for breast carcinoma may include a unilateral, fixed, firm, nontender lesion or lesion that is irregular or located eccentrically to the nipple-areola complex.[2]

There is a wide differential for the cause of gynecomastia, including physiological states related to age (three distinct peaks during infancy, puberty, and mid-late adulthood); effects from medications such as antipsychotics, antihypertensives, and antiandrogens; issues with androgen production, effect, or synthesis; increased estrogen production; and a host of other conditions, including obesity, liver and renal disease, and thyrotoxicosis.[2] In up to 25% of cases, there is no detectable abnormality.[13]

To further investigate the cause of gynecomastia, you perform laboratory investigations, which reveal a normal luteinizing hormone and follicle stimulating hormone, thyroid stimulating hormone (TSH), and fasting glucose. Serum testosterone is low normal at 249 ng · dL^{-1} (male ref: 250–827 ng · dL^{-1}) and prolactin is mildly elevated at 121 ng · mL^{-1} (male ref: 2.0–18.0 ng · mL^{-1}). A repeat prolactin was similar at 124 ng · mL^{-1}.

2. Given the above laboratory findings, what would be your next step?

A. Order a computed tomography of the head.
B. Order a pituitary magnetic resonance imaging (MRI).
C. Arrange for an urgent breast ultrasound/mammography.
D. Reassurance and observation.

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ANSWER/DISCUSSION

2. B. Laboratory investigations reveal a mild hyperprolactinemia and borderline testosterone. Potential causes of this abnormality include medication use, renal failure, thyroid disorders, parasellar tumors, and acromegaly.[12] Given the fact that your patient is otherwise healthy with normal TSH/T4, insulin-like growth factor 1, and renal labs, and takes no medication, a parasellar tumor is next to be ruled out. The most sensitive and specific way to visualize the sellar area, and in particular the pituitary, is by obtaining a gadolinium-enhanced MRI.[11] If unable to undergo MRI, contrast computed tomography is an alternative, but is less effective in revealing small adenomas. A breast ultrasound or mammography is unlikely to be necessary in this case but would be useful if there was a unilateral lesion, suspicious characteristics of the breast growth on history or physical, or a family history of breast cancer.

An MRI was performed and showed a 4-mm microadenoma in the right pituitary, with a midline pituitary stalk and normal optic chiasm.

3. Given the above laboratory and imaging findings, what is the most likely diagnosis?

A. Nonfunctioning pituitary adenoma.
B. Microprolactinoma.
C. Pituitary carcinoma.
D. Primary hypogonadism with incidentaloma.

ANSWER/DISCUSSION

3. B. Pituitary tumors represent 10–15% of all benign intracranial masses, of which 90% are pituitary adenomas.[11] While not all clinically significant, the prevalence of pituitary adenomas has been reported in radiological and autopsy studies to be as high as 20%.[5] Pituitary adenomas are benign lesions in the anterior pituitary that have three bases of classification: primary cell origin, functionality (hormone secreting or nonfunctioning), and size ($\geq$ 10 mm = macroadenoma, < 10 mm = microadenoma).[9] Based on imaging and laboratory investigations, this boom operator has a microprolactinoma. Prolactinomas constitute 40–50% of all adenomas and may present with a clinical syndrome of hyperprolactinemia.[9] Keeping in mind that serum prolactin levels correlate to tumor size, not all microprolactinomas will present symptomatically and may be discovered incidentally.[17] Symptoms in males can be manifested as a secondary hypogonadism and can include decreased libido, infertility, impotence, galactorrhea, and gynecomastia.[17]

Pituitary carcinoma is extremely rare, accounting for only 0.5% of symptomatic pituitary lesions.[7] Primary hypogonadism would have likely presented with an increased luteinizing hormone/follicle stimulating hormone and low testosterone with physical exam findings of hypogonadism.[13]

After diagnosing a pituitary adenoma, you place your patient on duties not including flying while obtaining an Endocrinology consultation. Nonfunctioning or small prolactinomas in asymptomatic patients do not require immediate treatment but do warrant monitoring.[8] Three primary treatment goals for treatment are to decrease hormone hypersecretion, decrease tumor size, and correct hormone deficiencies.[9] First-line treatment is considered medical management with a dopamine agonist (DA), of which bromocriptine and cabergoline are approved for this usage in the United States.[11] Surgical interventions are most often considered in individuals who are resistant to or intolerant of medical therapy or in those who have larger lesions or neurological compromise.[18]

4. Other than hormone effects, what other potential symptoms of a pituitary adenoma may cause aeromedical concern?

A. Mass effect impacting visual fields or cranial nerves.
B. Headaches.
C. Risk of apoplexy.
D. Hypopituitarism.
E. Side effects of first-line medication.
F. All of the above.

ANSWER/DISCUSSION

4. F. While many prolactinomas first present with effects of hormone hypersecretion, there is potential to produce mass effects as well. Due to the location of the pituitary gland, expansion of a pituitary tumor is limited posteriorly by the sella turcica. Any expansion of tissue in this space may expand to compress the optic chiasm, or optic nerve. If the optic chiasm is affected, the most common visual defect is a bitemporal hemianopia, and more severe compression of the optic nerve can lead to decreased visual acuity.[9] There is also potential to expand into the cavernous sinus, which could affect cranial nerves III, IV, and VI. Headaches are a common symptom unrelated to tumor size. Pituitary apoplexy (hemorrhage) is extremely rare, but is likely to cause sudden incapacitation if it occurs.[17] The most commonly used DAs for this condition, bromocriptine and cabergoline, have many side effects that are concerning for aviation, including nausea, orthostasis, drowsiness, fatigue, and the association with development of an impulse control disorder (ICD).[15] While the evidence for an ICD occurring after initiation of a DA comes mostly from the use of pramipexole and ropinirole in Parkinson's disease patients, there have been several case reports of ICDs in people with prolactinomas treated with bromocriptine or cabergoline.[1,3]

After assessment by Endocrinology, your boom operator elects to start cabergoline, as it is often better tolerated than bromocriptine, is often more effective, and has a longer half-life, which only requires twice a week dosing.[15] Repeat prolactin levels are decreasing and within 12 mo are normal. His testosterone is now mid-range and libido has increased. However, the gynecomastia remains unchanged. After 6 to 12 mo, gynecomastia likely demonstrates fibrosis and may not improve even with medical management of the prolactinoma.[13] He is seen by a plastic surgeon, who completes an excision with suction-assisted lipectomy bilaterally. One year after his initial presentation, the boom operator feels great, reports no medication side effects, and has no recurrence of gynecomastia. His repeat prolactin is now normal at 17 ng $\cdot$ dL^{-1}, and a repeat MRI shows a 2-mm pituitary lesion. Formal visual field testing and fundoscopic exam are normal. He is eager to

return to flying and wants to know what he needs to do to make this happen.

5. What is your aeromedical disposition of the patient at this time?

A. Return to full flying duties as he is asymptomatic and has no medication side effects.
B. Cease medication due to potential side effects and return to flying duties during this visit.
C. Refer to the Aeromedical Consultation Service (ACS) for their recommendation.
D. In conjunction with Endocrinology, discontinue cabergoline and observe for maintained remission for 6 mo, then submit to the ACS for consideration of a waiver.

ANSWER/DISCUSSION

5. D. Guidelines suggest remaining on a dopamine agonist for 2 yr before consideration of medication cessation, especially in the case of macroadenomas.[15] However, cessation of treatment after 1 to 3 yr has shown sustained remission in up to one-quarter of patients.[4] Therefore, in consult with Endocrinology, your patient may be a candidate for a trial cessation of cabergoline, as he is asymptomatic with a normal prolactin level, has only a very small tumor on MRI that has decreased in size by 50%, and has a strong desire to return to flying. Your patient decides to taper and discontinue the DA with the hope that sustained remission will allow him to submit for a waiver and return to flying.

The U.S. Air Force Waiver Guide states that secreting prolactinomas are potentially waiverable for all flying classes if they are asymptomatic and require no pharmacotherapy, or in trained aviators if pharmacotherapy has been discontinued and remission is sustained for 6 mo. For a wavier to be considered, the ACS requires an MRI, prolactin level, baseline formal visual field testing, dilated fundoscopy, and an Endocrinology consult. If a waiver is granted, renewal will require an updated Endocrinology consult and MRI annually for the first 2 yr, then every 2 yr if stable, and repeat formal visual field testing if the tumor size has increased or there are visual complaints.[10]

The U.S. Navy Aeromedical Reference and Waiver Guide states that all microadenomas may be considered for a waiver with provision of an Endocrinology consult, fasting blood sugar, prolactin, TSH, and insulin-like growth factor. An elevated prolactin is to be discussed with the Naval Aerospace Medical Institute. There is no waiver potential for the use of bromocriptine, but cabergoline may be considered for waiver after a 6-mo observation period. Waiver candidates must follow up with Endocrinology annually and undergo an annual MRI for 5 yr.[14]

Within the U.S. Army, this boom operator would be considered for waiver of a pituitary tumor provided sequelae are within acceptable limits. Specifically, for prolactinomas, aviators may be eligible for a waiver while treated with a stable dose of bromocriptine once the initial side effects subside. A waiver would require an Endocrinology consult and visual field studies.[16]

While not specifically mentioned in the Federal Aviation Administration Guide for Aviation Medical Examiners, pituitary adenomas will be reviewed on a case-by-case basis for consideration of a special issuance upon receipt of a current neurological evaluation, brain MRI, formal visual field testing, prolactin levels, and medication list. The use of cabergoline may be acceptable after a successful ground trial (O'Brien D. Federal Aviation Administration, Medical Policy and Standards. Personal communication; 2018).[6]

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REFERENCES

1. Barake M, Klibanski A, Tritos NA. Management of endocrine disease: impulse control disorders in patients with hyperprolactinemia treated with dopamine agonists: how much should we worry? Eur J Endocrinol. 2018; 179(6):R287–R296.
2. Braunstein GD. Clinical practice. Gynecomastia. N Engl J Med. 2007; 357(12):1229–1237.
3. Celik E, Ozkaya HM, Poyraz BC, Saglam T, Kadioglu P. Impulse control disorders in patients with prolactinoma receiving dopamine agonist therapy: a prospective study with 1 year follow-up. Endocrine. 2018; 62(3):692–700.
4. Dekkers OM, Lagro J, Burman P, Jørgensen JO, Romijn JA, Pereira AM. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab. 2010; 95(1):43–51.
5. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, et al. The prevalence of pituitary adenomas: a systemic review. Cancer. 2004; 101(3):613–619.
6. Federal Aviation Administration. Guide for aviation medical examiners. Washington (DC): Federal Aviation Administration; 2018. [Accessed 1 Dec. 2018]. Available from https://www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/.
7. Kaltsas GA, Nomikos P, Kontogeorgos G, Buchfelder M, Grossman AB. Clinical review: diagnosis and management of pituitary carcinomas. J Clin Endocrinol Metab. 2005; 90(5):3089–3099.
8. Klibanski A. Clinical practice. Prolactinomas. N Engl J Med. 2010; 362(13):1219–1226.
9. Lake MG, Krook LS, Cruz SV. Pituitary adenomas: an overview. Am Fam Physician. 2013; 88(5):319–327.
10. Martin B, Van Syoc D. Pituitary tumors (Aug. 2016). In: Air Force waiver guide. Wright-Patterson AFB (OH): U.S. Air Force School of Aerospace Medicine; 2018:642–650. [Accessed 10 Nov. 2018]. Available from https://www.wpafb.af.mil/afrl/711hpw/.
11. Melmed S. Pituitary tumors. Endocrinol Metab Clin North Am. 2015; 44(1):1–9.
12. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96(2):273–288.
13. Morcos RN, Kizy T. Gynecomastia: when is treatment indicated? J Fam Pract. 2012; 61(12):719–725.
14. Naval Aerospace Medical Institute. 5.6. Pituitary tumors. In: U.S. Navy aeromedical reference and waiver guide. Pensacola (FL): Naval

Aerospace Medical Institute; 2018. [Accessed 10 Nov. 2018]. Available from http://www.med.navy.mil/sites/nmotc/nami/arwg/Pages/default.aspx.
15. Schlechte JA. Clinical practice. Prolactinoma. N Engl J Med. 2003; 349(21):2035–2041.
16. U.S. Army Aeromedical Activity. Pituitary tumors (ICD9 194.3). In: Flight surgeon's aeromedical checklists. Aeromedical policy letters. Ft. Rucker (AL): U.S. Army Aeromedical Activity; 2014. [Accessed 10 Nov. 2018]. Available from https://glwach.amedd.army.mil/victoryclinic/documents/Army_APLs_28may2014.pdf.
17. Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. J Clin Neurosci. 2015; 22(10):1562–1567.
18. Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 2: Treatment and management strategies. J Clin Neurosci. 2015; 22(10):1568–1574.