Index of Suspicion

4 Gynecomastia in a 15-year-old Boy

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PRESENTATION

A 15-year-old boy is evaluated for gynecomastia that has continued to increase in size and discomfort during the past year. In addition, he also has moderate to severe acne that has not improved with topical therapies and systemic antibiotic drugs. He reports having some general fatigue as well as increased appetite, and he has gained 13 lb (5.9 kg) in the previous 7 months. There has been no fever, and apart from occasional headaches, he has no other complaints of pain. His personal and family medical history is otherwise normal. His only medications are minocycline and topical isotretinoin and clindamycin to treat his acne.

On physical examination the blood pressure is 156/98 mm Hg. He has extensive acne on his face, upper chest, and back. Examination of the breasts shows bilateral and mildly tender gynecomastia, with fibroglandular tissue measuring 10 cm in the right breast and 9 cm in the left, and both having secondary mounds (Fig 1). No galactorrhea is present. His abdominal examination findings are normal, and he has Tanner V genitalia with normal testes. Based on the history and physical examination findings, blood testing and subsequent imaging are performed and lead to the correct diagnosis.

DISCUSSION

Diagnosis

The combination of progressive gynecomastia coupled with extensive acne and hypertension in an adolescent male suggested excessive hormone production. This suspicion was confirmed by the finding of elevated serum estradiol, estrone, and dehydroepiandosterone sulfate (DHEA-S) levels ranging from 4 to 30 times the upper limit of normal. In addition, the patient had an elevated 24-hour urine cortisol level, with suppression of serum corticotropin. These findings in an adolescent male are consistent with the presence of a hormone-secreting tumor in the adrenal gland. Accordingly, magnetic resonance imaging (MRI) of the abdomen was performed and demonstrated an 8×7×7-cm mass arising in the right adrenal gland (Fig 2). He underwent a gross total excision of this mass, with pathology confirming the diagnosis of adrenocortical adenoma.

AUTHOR DISCLOSURE Ms Walls and Drs Smith, Draus, and Wagner have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

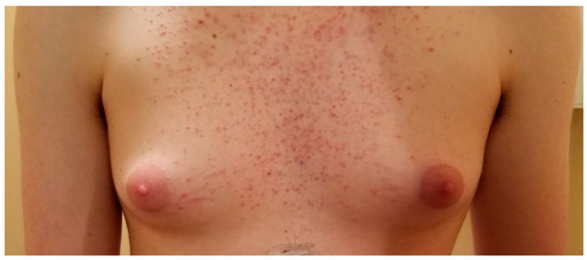

Figure 1. Demonstration of acne and gynecomastia in the 15-year-old boy described in the case.

The Condition

Feminizing adrenocortical tumors (FATs) are defined as adrenal neoplasms that secrete estrogen with or without other adrenal hormones. These tumors are quite rare, accounting for less than 2% of all adrenal neoplasms, with two-thirds occurring in adults and one-third in children. In children, both sexes are represented somewhat equally, with a median age of 5 years. (1) Most FATs are malignant adrenocortical carcinomas, although some are histologically benign adenomas, as seen in our patient. Male patients present with gynecomastia, and in some patients testicular atrophy and breast tenderness are also noted. The presence of acne and hypertension is related to the concomitant secretion of glucocorticoids and DHEA-S.

Management

Primary care physicians often encounter breast enlargement in males, and it is critical to distinguish when gynecomastia is part of normal development and when there may be underlying pathology. Physiologic gynecomastia is defined as the normal transient glandular proliferation of breast tissue during the teenage years. This process occurs most often in mid-puberty with Tanner stage 3 or 4 pubic hair, and in the first few months the breast tissue may be mildly tender. One likely cause for physiologic gynecomastia is a temporary imbalance in the free androgen to free estrogen ratio that allows for greater estrogen effects on breast tissue. As puberty progresses, circulating androgen levels rise and alter the previous ratio with estrogen, leading to resolution of gynecomastia within 1 to 3 years in 90% of boys. The proper physical examination technique is essential for the assessment of gynecomastia, and this consists of compressing the glandular tissue between the thumb and forefinger while the patient is supine and holding the hands behind the head.

Indications that gynecomastia is pathologic include prepubertal age, fibroglandular tissue measuring greater than 4 cm, rapid progression, or other abnormalities on physical examination, such as galactorrhea, hypertension, acne, or abnormal testes. In our patient, the presence of progressive gynecomastia of glandular tissue at least 8 cm coupled with severe acne and hypertension was clearly not physiologic and warranted further evaluation.

The focused evaluation of pathologic gynecomastia is directed by the history and physical examination findings. Key historical information includes the duration of symptoms and the presence of nipple discharge or testicular swelling. Important features of the medical history include the presence of an undescended testicle, previous mumps infection, or previous liver, renal, or thyroid disease. The medication history should be reviewed carefully given that certain prescription medicines (eg, ranitidine, ketoconazole) as well as illicit substances (eg, marijuana, anabolic steroids) have been associated with gynecomastia.

The presence of estrogen excess may be confirmed by finding high estradiol and estrone levels, as seen in our patient. Assessment of human chorionic gonadotropin (hCG) should be included as well because some patients with Leydig or Sertoli cell tumors of the testes may secrete hCG that results in preferential estrogen production by the

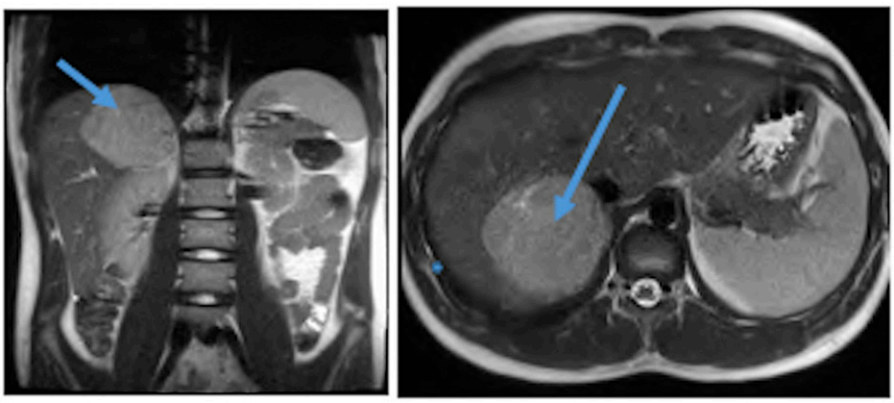

Figure 2. T2-weighted magnetic resonance imaging demonstrating a large mass (arrows) arising in the right adrenal gland as seen on coronal and axial projections.

testes. (2) This association is most commonly seen in patients with Peutz-Jeghers syndrome, which is characterized by mucosal hyperpigmentation and colonic polyps. Because testicular masses may sometimes be difficult to appreciate on physical examination, testicular ultrasonography is indicated on any male patient with gynecomastia and an elevated hCG level. However, our patient had no mucosal hyperpigmentation, and the hCG level and testicular examination findings were both normal, helping us rule out the testes as the source of estradiol production. The normal testicular examination findings coupled with a normal testosterone level, low luteinizing hormone level, and normal body habitus also made hypogonadism from Klinefelter syndrome less likely. Similarly, the finding of a normal free thyrotropin level and absence of any examination findings of hyperthyroidism helped rule out this unusual but important cause of gynecomastia.

The presence of hypertension and acne in our patient raised the possibility of excess glucocorticoid or androgen levels. This was confirmed with the finding of an elevated 24-hour urine cortisol level, as well as elevation of the serum DHEA-S level. Test results of other hormones that may be associated with hypertension, such as aldosterone, plasma renin activity, and metanephrines, were all normal.

Given that our laboratory evaluation pointed to an adrenal mass as the likely cause for the high levels of estradiol, cortisol, and DHEA-S, we obtained MRIs of the abdomen. This identified a mildly enhancing lesion arising in the right adrenal gland, with no evidence of infiltration into surrounding structures or spread to regional lymph nodes. Computed tomography of the chest did not identify lung metastases. The size of the adrenal lesion raised concern that this may be a malignant adrenocortical carcinoma, and an open resection was performed.

The histologic determination of malignancy in adrenocortical neoplasms can be challenging, but using established guidelines for pediatric adrenal tumors allowed this patient's mass to be determined as a histologically benign adrenocortical adenoma. Specifically, the tumor had no malignant features such as cytologic atypia, necrosis, significant mitotic activity, or vascular invasion. Although some adult patients with feminizing adrenocortical carcinomas have fared poorly, FATs are so rare that prognosis is difficult to establish, particularly when malignant features are not identified. However, in a series of 83 children with adrenocortical tumors, patients identified as having benign adenomas using the previously mentioned histologic criteria were all surviving disease-free with mean follow-up of 14.7 years. (3) This is in contrast to children with similarly staged adrenocortical carcinoma, who have an estimated 5-year overall survival of only 40%. (4) Our patient remains in remission 21 months after being treated with surgery alone, and he is expected to have an excellent long-term prognosis. Adjuvant chemotherapy or radiotherapy is used only in patients with adrenocortical carcinomas who have high-risk features or metastatic disease. Of note, after surgery our patient experienced marked improvement in his 3 presenting symptoms (acne, hypertension, and gynecomastia), as well as normalization of his estradiol, estrone, and DHEA-S levels.

Pediatricians commonly encounter acne in adolescents, which is related to the physiologic production of sebum in response to hormonal stimulation. Our patient had a limited response to topical and oral antibiotic drugs, as well as topical isotretinoin. In patients with acne not responsive to oral or topical antibiotic agents, monitoring for signs of glucocorticoid excess, such as hypertension, is important. In retrospect, our patient had blood pressures exceeding the 90th percentile for age (139/80 mm Hg) on a few primary care visits during the year before diagnosis of his adrenal mass. It is important for primary care physicians to recognize hypertension, and identification of hypertension can now be enhanced by clinical decision support software that can be included in electronic records. (5) Although the isolated finding of an elevated blood pressure may be readily explained by pain or anxiety, continued monitoring is important to identify whether this is a persistent problem, and if so, whether other conditions are associated.

Although gynecomastia, acne, and hypertension are commonly encountered by primary care physicians, their coexistence and severity in this patient clearly suggested more significant underlying pathology. Guided by the history and physical examination, laboratory testing helped identify the adrenal gland as the source of these symptoms, leading to appropriate imaging and surgical intervention that has resulted in a successful outcome.

Lessons for the Clinician

- Although physiologic gynecomastia is common in mid-adolescence, the finding of rapidly progressive fibroglandular breast tissue greater than 4 cm is abnormal and warrants further evaluation.
- Evaluation of gynecomastia in adolescent males should begin with a careful review of systems and medication history, followed by a comprehensive physical examination that includes attention to vital signs, skin findings, pubertal status, and testicular findings.
- Feminizing tumors in children are rare and may arise from adrenal or genital origin.
- Patients with feminization should have evaluation of estradiol, testosterone, and human chorionic gonadotropin

levels, and dehydroepiandosterone sulfate and cortisol levels should be assessed in those with evidence of glucocorticoid excess.

- Careful histologic evaluation of adrenocortical tumors can help characterize them as either benign adenomas or malignant carcinomas, which has both prognostic and management implications.

References and Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/41/4/206.

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Suggested Readings

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