Visual Diagnosis: An Adolescent Female Who Has Increasing Hair Growth
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Presentation
A 14-year-old girl presents to the clinic complaining of increasing hair growth on her face and trunk for the past 2 years. Her parents note that her normally low-pitched voice has seemed even lower the past few months. Breast and pubic hair development began at 11 years of age, and menstrual periods began at approximately 12 years of age. Menstrual periods occur every 4 to 8 weeks. The girl is in good health, has never had any serious illness, and denies taking any medications. She has always been the tallest in her class.

Physical examination reveals a well-nourished female who has a deep voice, receding frontal hairline, and conspicuous, dark hair over the upper lip and chin (Fig. 1). Minimal facial acne is noted. Vital signs include a temperature of 98°F (36.7°C), respiratory rate of 22 breaths/min, pulse of 90 beats/min, and a blood pressure of 130/70 mm Hg. Height is 166.9 cm (50th to 75th percentile) and weight is 67.7 kg (90th to 97th percentile). Breast examination reveals elevation of the areola and nipple (Sexual Maturity Rating stage 4), with prominent dark hairs over the areola (Fig. 2). Truncal examination demonstrates midline hair over the chest and upper abdomen as well as a suggestion of increased muscle mass and loss of female contour (Fig. 3). Genitourinary inspection is remarkable for an enlarged clitoris, measuring 2.5 cm in length. Findings on the remainder of the physical examination are normal.

Serum testosterone and androstenedione levels are approximately five-fold higher than normal for her age. The serum dehydroepiandrosterone sulfate (DHEAS) concentration is normal. Serum progesterone and estradiol levels are normal. Serum follicle stimulating hormone (FSH) concentration is low, and luteinizing hormone (LH) concentration is normal. Human chorionic gonadotropin (hCG) measurement is normal.

Computed tomography (CT) of the pelvis suggests the diagnosis.
Figure 1. A 14-year-old female who has prominent facial hair.

Figure 2. Increased hair growth on areola and chest.

Figure 3. Truncal examination.
Diagnosis: Ovarian Tumor (Sertoli-Leydig Cell Tumor)

CT examination demonstrates a 6-cm long tumor of mixed solid and cystic appearance in the right ovary (Fig. 4). Serum alpha-fetoprotein (AFP) level is elevated. A right oophorectomy reveals a Sertoli-Leydig tumor of intermediate differentiation confined within the ovary. Six months after surgery, the patient's hirsutism is reduced markedly, and her menstrual periods occur in regular, monthly cycles (Fig. 5).

Definitions

Hirsutism and virilization are terms frequently used to describe excess hair growth in women. Normally, distribution of hair depends on age and gender. Fine, lightly pigmented hairs, known as vellus hair, cover most of the body. Coarse, darker pigmented hairs, known as terminal hair, grow in the eyebrows, eyelashes, and scalp. During puberty, under the influence of androgens, terminal hair replaces vellus hair in the axillae, lower pubic triangle, arms, and lower legs of both genders. In adult men, terminal hair also develops in the androgen-sensitive regions of the upper lip, chin, sideburns, upper arms, chest (periareolar area and linea alba), upper pubic triangle, thighs, and intergluteal region. In adult women, androgen excess or increased androgen sensitivity may lead to a similar hair distribution.

Hirsutism in women is defined as excess body hair in male-pattern distribution. Virilization is the concurrent presentation of hirsutism with other signs of androgen excess, including frontotemporal alopecia (male-pattern balding), deepening of the voice (laryngeal hypertrophy), a decrease in breast size, clitoral hypertrophy, increased muscle mass, and amenorrhea or oligomenorrhea. Acne often accompanies androgen excess. Hirsutism may be the first manifestation of a condition that may lead to virilization. (Of note, hypertrichosis describes an excess of vellus hair.)

Androgens affect the pilosebaceous unit, leading to increased activity of the hair follicle and sebaceous gland (development of terminal hair and acne). Serum androgens include testosterone, free testosterone, dehydroepiandrosterone (DHEA), DHEAS, and androstenedione. Testosterone is converted to dihydrotestosterone (DHT) in the skin and the hair follicle by 5-alpha-reductase. In women, approximately 50% of circulating androgens arise from the ovaries and adrenals, with the ovary as a source of testosterone, androstenedione, and DHEA and the adrenal as a source of androstenedione, DHEA, and DHEAS. Androstenedione from the adrenal is converted peripherally to testosterone. Ovarian androgen production is gonadotrophin-dependent; adrenal androgen production is adrenocorticotropic hormone-dependent.

Figure 4. Pelvic CT demonstrating a cystic solid mass in the right ovary. (Courtesy of Ulrich V. Willi, MD)

Figure 5. Six months after oophorectomy.
(ACTH)-dependent. Most of the circulating testosterone and DHT is bound to sex hormone-binding globulin (SHBG). A decrease in SHBG levels leads to a relative increase in free testosterone.

Etiology
Hirsutism can result from excess androgen production, relative circulating androgen excess due to low levels of binding globulins, excess end-organ response, or patient perception. The evaluation should assess whether hirsutism is accompanied by associated pilosebaceous unit overactivity, ovulation disorder, or signs of virilization. In young women, most cases of virilization are acute and result from increased adrenal or ovarian androgen production, a decrease in SHBG, or the use of exogenous androgens.

Differential Diagnosis
For disorders of excess androgen, the differential diagnosis includes exogenous androgens, disorders of the ovary or adrenal, and disorders of sexual differentiation (mixed gonadal dysgenesis). Disorders of the ovary include polycystic ovary syndrome (PCOS), severe insulin resistance, hyperthecosis, tumors, and enzyme deficiency. Features of PCOS, the most common cause of acute hirsutism in adolescent females, include hirsutism with obesity, insulin resistance, acanthosis nigricans (velvety, thickened hyperpigmentation of the axillae, neck, anogenital area, and groin), oligomenorrhea, anovulation, and infertility. Disorders of the adrenal include late-onset congenital adrenal hyperplasia, Cushing syndrome, and tumors.

Drugs (anabolic steroids, minoxidil, acetazolamide, danazol, valproate, glucocorticoids), pregnancy, anorexia nervosa, hypothyroidism, and malnutrition may cause relative circulating androgen excess due to low binding globulins.

Genetic, idiopathic, familial, or racial factors may cause excess end-organ response to androgens.

Examination
The history and physical examination help determine the cause of hirsutism. It is important to note the patient’s ethnic background; body perception; menstrual history; drug history; and the age of onset, progression, and duration of hirsutism. The physical examination should include evaluation of height and weight, blood pressure, body habitus, and pubertal development. Past photographs may help assess changes in body habitus. Use of subjective clinical scoring systems, such as the Feriman Gallwey scale, help measure the degree of conversion of vellus to terminal hair. An abdominal examination may reveal a palpable mass. Other physical signs suggestive of androgen excess are acne, acanthosis nigricans, galactorrhea, central obesity, and striae.

Laboratory evaluation is warranted if physical examination reveals virilization and the presence of exogenous androgens is ruled out. Elevated serum total and free testosterone levels may reveal endogenous androgen excess from the ovary or adrenal. An elevated serum DHEAS level indicates adrenal pathology. An elevated fasting 17-hydroxyprogesterone level may indicate congenital adrenal hyperplasia (CAH). Often, an ACTH stimulation test is required to diagnose late-onset CAH. Abnormal FSH or LH levels may reveal an ovulation disorder; a high LH concentration is suggestive of PCOS. Normal gonadotropin levels do not, however, rule out PCOS. Suppressed gonadotropins, as in this case, strongly suggest either exogenous administration or autonomous overproduction of androgens from a tumor. Pelvic imaging studies, including ultrasonography, CT, or magnetic resonance imaging, may reveal an underlying tumor.

Treatment
Treatment of isolated hirsutism in an adolescent focuses on preventing further stimulation of hair growth by decreasing androgen levels (eg, metformin administration), increasing SHBG (eg, estrogen administration), or blocking androgen action (eg, spironolactone administration). Cosmetic correction of already stimulated hair often is necessary. Virilization in an adolescent frequently indicates a malignant process that requires surgery. Sertoli-Leydig cell tumor of the ovary, previously termed androblastoma or arrhenoblastoma, is a sex cord-
stromal tumor that accounts for 0.5% of all ovarian tumors. Ovarian Sertoli-Leydig cell tumor is classified into five histologic categories: well-differentiated, intermediately differentiated, poorly differentiated, retiform, and mixed. Younger patients tend to have more poorly differentiated tumors. Age at presentation ranges from 7 to 79 years, with the average being 25 years. Clinical symptoms include amenorrhea, abdominal mass, virilization, and in young children, heterosexual precocity. The tumor marker AFP may be elevated. Treatment consists of surgical excision, chemotherapy, or both, depending on staging. The prognosis generally is good.

Summary
Hirsutism affects the well-being of adolescent women and may be the manifestation of a serious underlying disorder. Virilization, if present, requires a prompt, thorough, and comprehensive diagnostic evaluation.

Comment: Although ovarian tumors are rare in adolescent females, PCOS is not. This case provides a good overview of the presentation and evaluation of hirsutism and its infrequent companion, virilization.

Joseph Zenel
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Suggested Reading
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