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## Case 29-2018: A 31-Year-Old Woman with Infertility

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### PRESENTATION OF CASE

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*Dr. Caitlin Sacha* (Obstetrics and Gynecology): A 31-year-old woman with infertility was referred to the fertility center of this hospital by a surrogate parenting agency to discuss the possibility of family building with an oocyte donor and a gestational carrier.

The patient reported that, when she was 16 years of age, she had been evaluated for primary amenorrhea and had received a diagnosis of congenital absence of the uterus and ovaries. When she was approximately 12 years of age, adrenarche and thelarche had occurred in association with a linear growth spurt. The patient had never had menstrual menses or any headaches, vision problems, galactorrhea, vasomotor symptoms, or reduction in exercise tolerance.

The patient also reported that, when she was 10 years of age, she had fractured her arm and had undergone tonsillectomy. She took no medications and had no known allergies. Four months before the current evaluation, she had moved to New England from northern Europe; she currently lived with her husband in a suburban area and worked in an office. She drank alcohol rarely, smoked 3 to 5 cigarettes a day, and did not use illicit drugs. Her mother had conceived her children easily and had undergone hysterectomy because of endometriosis when she was 46 years of age, and her maternal grandfather had died of a myocardial infarction when he was 70 years of age. The patient's father and two sisters were healthy; one sister was the patient's fraternal twin and had regular menses.

On examination, the blood pressure was 118/74 mm Hg, the weight 68.1 kg, the height 172.7 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 22.8. The patient had minimal body hair. A pelvic examination revealed normal female external genitalia and normal vaginal length and rugae; there was no abnormal vaginal discharge or evidence of pelvic-organ prolapse. The cervix and uterus were absent. There was mild fullness in the

**Table 1. Laboratory Data.\***

Variable	Reference Range, Women†	On Presentation	5 Days Later
Human chorionic gonadotropin (IU/liter)	<6	<6	
Follicle-stimulating hormone (IU/liter)	18.0–153.0 in postmenopause 3.0–20.0 in premenopause during the follicular phase 9.0–26.0 in premenopause during the ovulatory phase 1.0–12.0 in premenopause during the luteal phase	1.9	2.1
Luteinizing hormone (IU/liter)	16.0–64.0 in postmenopause 2.0–15.0 in premenopause during the follicular phase 22.0–105.0 in premenopause during the ovulatory phase 0.6–19.0 in premenopause during the luteal phase		25.5
Estradiol (pg/ml)	<50 in postmenopause 27–156 in premenopause during the follicular phase 48–314 in premenopause during the ovulatory phase 33–298 in premenopause during the luteal phase	49	43
Progesterone (ng/ml)	<0.20–1.40 in postmenopause <0.20–1.50 in premenopause during the follicular phase 0.80–3.00 in premenopause during the ovulatory phase 1.70–27.00 in premenopause during the luteal phase	2.15	1.98
Prolactin (ng/ml)	0.1–23.3	6.4	
Thyrotropin ( $\mu$ IU/ml)	0.40–5.00	1.42	
Free thyroxine (ng/dl)	0.9–1.8	1.3	

\* To convert the values for estradiol to picomoles per liter, multiply by 3.671. To convert the values for progesterone to nanomoles per liter, multiply by 3.180. To convert the values for free thyroxine to picomoles per liter, multiply by 12.87.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for women who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

left adnexal region, without tenderness or a discrete mass. The remainder of the physical examination was normal.

Ultrasonography of the pelvis confirmed the absence of the uterus and cervix. The right ovary was not visualized; there were clusters of simple cysts in the adnexal region on the right side (one measuring 24 mm by 25 mm and another measuring 18 mm by 17 mm) and on the left side (one measuring 18 mm by 17 mm and another measuring 20 mm by 21 mm). Tests were positive for rubella virus IgG antibodies and varicella-zoster virus IgG antibodies, and screening tests were negative for hepatitis B virus surface antigen, human immunodeficiency virus types 1 and 2, hepatitis C virus, human T-lymphotropic virus types 1 and 2, syphilis, and cytomegalovirus. The complete blood count and white-cell differential count were normal; other laboratory test results are shown in Table 1. Blood specimens were collected for measurement of the antimüllerian hormone level and for chromosome analysis.

Five days later, additional diagnostic tests were performed; laboratory test results are shown in Table 1. Dual-energy x-ray absorptiometry was performed for the assessment of bone mineral density. There was borderline low bone mass in the spine on posterior–anterior examination (bone mineral density T score,  $-1.10$ ), normal bone mass in the vertebral bodies on lateral examination (T score,  $-0.20$ ), and normal bone mass in the femoral neck (T score,  $-0.90$ ).

Four days later, a diagnostic test result was received, and management decisions were made.

#### DIFFERENTIAL DIAGNOSIS

*Dr. Christos Coutifaris:* This 31-year-old woman with primary amenorrhea had been told when she was 16 years of age that she had no uterus or ovaries. She had had a growth spurt and normal thelarche and adrenarche when she was 12 years of age. On physical examination, the height was 172.7 cm (>90th percentile for women), the vaginal length was normal, and no uterus or

cervix was present. On the basis of these findings, it is likely that her underlying disorder stemmed from an abnormality of sexual differentiation.

To provide context for a discussion of the differential diagnosis, it is useful to first review the process of sexual differentiation (Fig. 1). Gonadal differentiation depends on the presence or absence of a Y chromosome and specifically on expression of the SRY gene, which maps to the short arm of the Y chromosome (Yp). Expression of SRY mediates the development of the undifferentiated gonad into a testis. Then, fetal testosterone secretion occurs, leading to the development of the wolffian ducts and ultimately to a typical male genital phenotype. In addition, secretion of antimüllerian hormone by the Sertoli cells of the fetal testis induces regression of the müllerian ducts. In the absence of a Y chromosome (and SRY expression) and in the presence of two intact X chromosomes, female gonadal and phenotypic differentiation occurs, with ovarian development, a typical female genital phenotype, and reproductive function of typical onset and duration.<sup>1</sup> At which point might the typical process of sexual differentiation have gone awry in this patient?

#### STEROIDOGENIC ENZYME DEFECTS IN AN XY GENOTYPE

Defects of enzymes involved in early steroidogenesis in the context of an XY genotype may lead to a clinical phenotype similar to that seen in this patient.<sup>2</sup> In  $17\beta$ -hydroxysteroid dehydrogenase deficiency, androstenedione (a weak androgen) is synthesized but testosterone is not. Because the fetus is not exposed to a potent androgen, typical male genital differentiation does not occur. However, patients with  $17\beta$ -hydroxysteroid dehydrogenase deficiency usually undergo virilization during puberty if the testes have not been removed, and such virilization was not seen in this patient.

A deficiency of P450c17, an enzyme complex that mediates the activity of both  $17\alpha$ -hydroxylase and  $17,20$ -lyase, would lead to profound fetal androgen deficiency. Patients with this condition have female external genitalia at birth, as did this patient. However, patients with this condition would be expected to present with an adre-

nal crisis early in life because the synthesis of mineralocorticoids would be impaired. Milder deficiencies of P450c17 can result in delayed puberty, hypokalemia, and hypertension. Overall, given the absence of relevant clinical characteristics in this patient, these steroidogenic enzyme defects can be ruled out.

#### COMPLETE XY GONADAL DYSGENESIS

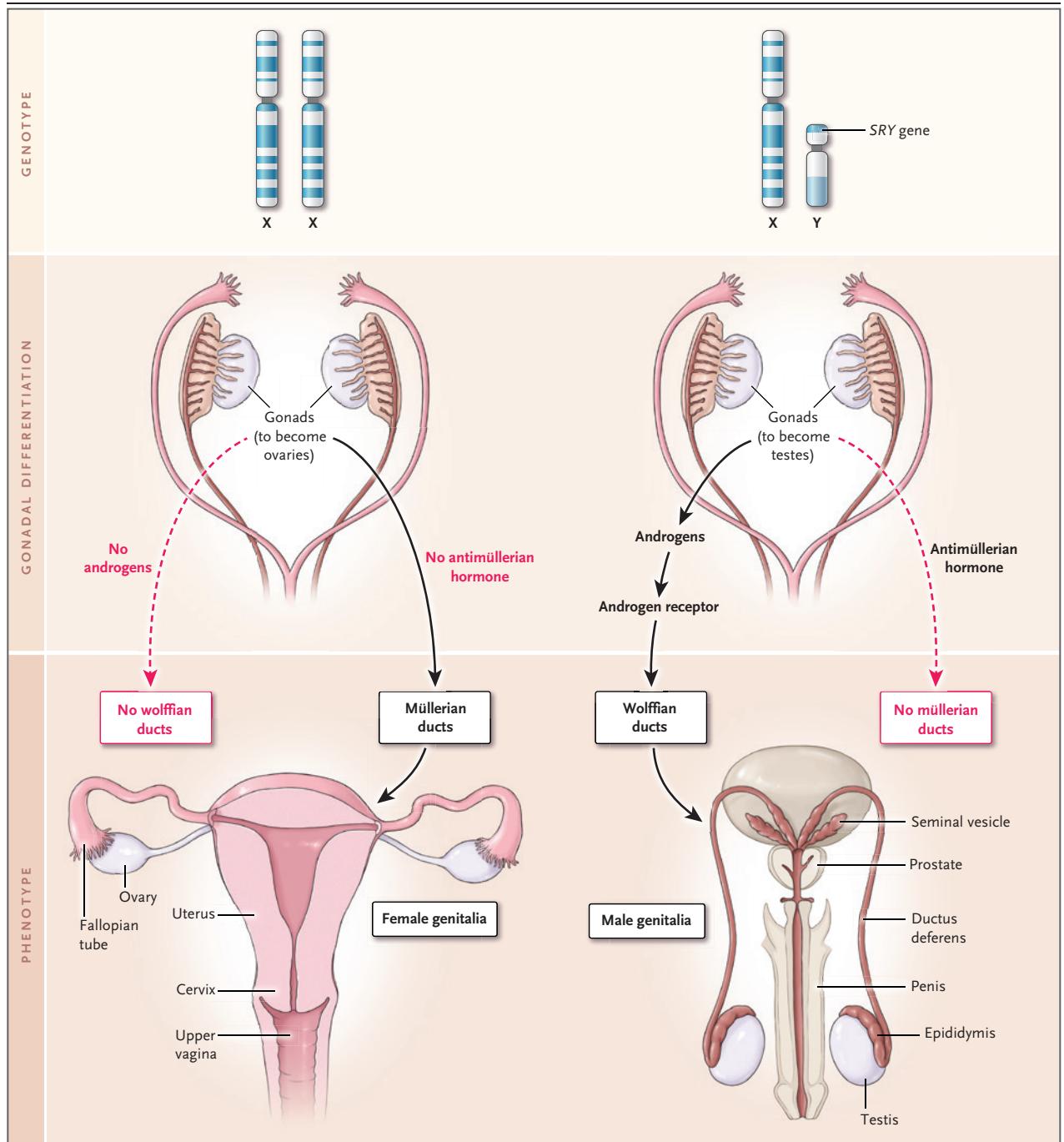
Another diagnostic consideration in this case is complete XY gonadal dysgenesis (known as the Swyer syndrome), which results from the absence of the SRY gene or its gene product.<sup>3</sup> When SRY is absent, the testis is also absent, and patients with complete XY gonadal dysgenesis have streak gonads, which are devoid of germ cells, and internal müllerian structures, including a hypoplastic uterus and cervix. The clinical presentation may include delays in breast development, puberty, and menarche. The diagnosis is usually made at birth or during childhood, and gonadal excision is recommended because of an associated risk of gonadal cancers.<sup>4</sup> Given the absence of a uterus and cervix in this patient, the diagnosis of complete XY gonadal dysgenesis can be ruled out.

#### $5\alpha$ -REDUCTASE DEFICIENCY

The diagnosis of  $5\alpha$ -reductase deficiency should also be considered in this case.<sup>5</sup>  $5\alpha$ -Reductase is an enzyme that converts testosterone to dihydrotestosterone, the primary active hormone in peripheral tissues that induces a male phenotype in the context of an XY genotype. Patients with  $5\alpha$ -reductase deficiency may have female genitalia at birth, but the genitalia are often ambiguous because of the high levels of testosterone. In addition, in patients with  $5\alpha$ -reductase deficiency, there is the potential for virilization at puberty, which was not observed in this patient.

#### LEYDIG-CELL HYPOPLASIA

Leydig-cell hypoplasia results from a mutation that inactivates the G-protein-coupled luteinizing hormone receptor in the context of an XY genotype.<sup>6</sup> Such a mutation leads to a defect in fetal androgen production by Leydig cells, resulting in a female genital phenotype. However, secondary sexual characteristics do not develop and puberty does not occur in patients with



**Figure 1. Typical Gonadal and Phenotypic Sexual Differentiation.**

The presence of a Y chromosome and expression of the *SRY* gene lead to the development of the undifferentiated gonad into a testis. In turn, fetal androgen (testosterone) secretion leads to the development of the wolffian ducts and ultimately to a typical male genital phenotype. Secretion of antimüllerian hormone by the Sertoli cells of the fetal testis induces the regression of the müllerian ducts. In the absence of a Y chromosome (and *SRY* expression) and in the presence of two intact X chromosomes, female gonadal and phenotypic differentiation occurs, leading to ovarian development and a typical female genital phenotype.

Leydig-cell hypoplasia. Given that thelarche and adrenarche had been normal in this patient, Leydig-cell hypoplasia can also be ruled out.

#### MÜLLERIAN APLASIA

Patients with müllerian aplasia (known as the Mayer–Rokitansky–Küster–Hauser syndrome) have an XX genotype. They lack all derivatives of the müllerian ducts (fallopian tubes, uterus, cervix, and upper vagina) but have ovaries and undergo puberty, with appropriately timed breast development and growth of axillary and pubic hair.<sup>7-9</sup> Such patients are endocrinologically typical females, and they have typical female external genitalia at birth but have amenorrhea due to the absence of a uterus. Some cases are associated with specific gene deletions or sporadic mutations. In müllerian aplasia type 1, which is the most common type, only the reproductive organs are affected. Müllerian aplasia type 2 is associated with abnormalities in other parts of the body, such as the kidneys or skeleton. Müllerian aplasia is a plausible diagnosis in this patient, because it could explain the absence of a uterus and cervix in a patient with female external genitalia and normal thelarche and adrenarche.

#### ANDROGEN INSENSITIVITY SYNDROME

Another diagnostic consideration in this case is the androgen insensitivity syndrome.<sup>10-15</sup> Patients with this syndrome have an XY genotype and mutations in the androgen receptor gene, which is located on chromosome Xq1.1-1.2. Depending on the mutation, the cellular response that follows binding of androgens to their receptor varies and thus the clinical phenotype may be complete or partial. Patients with complete androgen insensitivity syndrome have testes and secrete high levels of androgens (particularly testosterone). However, because of the absence of a functional androgen receptor, there is no response to the hormones in peripheral tissues, either in utero or after puberty. As a result, the wolffian ducts do not develop. In parallel, the müllerian ducts regress owing to the secretion of antimüllerian hormone by Sertoli cells. Thus, patients with complete androgen insensitivity syndrome have female-appearing external genitalia but no uterus, cervix, or upper vagina, and they have cryptorchidism, with either intraabdominal testes

or testes at various stages of descent in the inguinal canal. In addition, they undergo puberty and breast development as a result of the peripheral conversion of androgens to estrogens by aromatase, but they have virtually no axillary or pubic hair. In contrast, in patients with partial androgen insensitivity syndrome, the external genitalia may be somewhat ambiguous at birth and partial virilization may occur during puberty. The clinical features seen in this patient are consistent with complete androgen insensitivity syndrome.

#### SUMMARY

On the basis of the history and findings on examination, the most likely diagnosis in this case is either müllerian aplasia or complete androgen insensitivity syndrome (Table 2). In a review of the laboratory data, the most interesting finding, which helps to distinguish between these two diagnoses, is the low level of follicle-stimulating hormone (FSH) noted on two separate measurements despite an elevated level of luteinizing hormone. This pattern of gonadotropin secretion would not be observed in females who have a normal menstrual cycle. Furthermore, if premature ovarian insufficiency were present, the FSH level would be elevated and would also be higher than the luteinizing hormone level, and both hormones would be at menopausal levels. In contrast, the low level of FSH is consistent with complete androgen insensitivity syndrome. As opposed to the regulation of luteinizing hormone, which is dependent solely on feedback from gonadal steroids, the regulation of FSH is dependent on feedback from both gonadal steroids and inhibin.<sup>16</sup> In complete androgen insensitivity syndrome, the low levels of circulating estrogens lead to minimal negative feedback and the high levels of androgens (particularly testosterone) do not lead to feedback that causes inhibition of gonadotropins, owing to the absence of a functional androgen receptor in the hypothalamus and anterior pituitary. However, Sertoli cells secrete copious amounts of inhibin B, which selectively inhibits FSH secretion by gonadotropic cells. Given that the FSH level was suppressed in this patient, I hypothesize that she had hypersecretion of inhibin B, possibly from a tumor. Maybe the fullness on the left side that

**Table 2. Findings in This Patient and Their Association with Müllerian Aplasia and Complete Androgen Insensitivity Syndrome.**

Finding in this Patient	Associated with Müllerian Aplasia	Associated with Complete Androgen Insensitivity Syndrome
Height, 172.7 cm (>90th percentile)	Yes; constitutional	Yes
Minimal body hair	Maybe; can be constitutional in patients of northern European heritage	Yes
Absence of ovaries on history and ultrasonography	Yes, if patient has premature ovarian insufficiency or streak gonads, but unlikely	Yes
Absence of uterus on examination and ultrasonography	Yes	Yes
Absence of cervix on examination and ultrasonography	Yes	Yes
Normal vagina on examination	Yes, if patient is sexually active	Yes, if patient is sexually active
Luteinizing hormone level, 25.5 IU/liter (moderately high)	Yes, if patient has premature ovarian insufficiency	Yes
Estradiol levels, 49 pg/ml and 43 pg/ml	Yes, if patient is anovulatory or has premature ovarian insufficiency	Yes
Progesterone levels, 2.15 ng/ml and 1.98 ng/ml	Yes, if patient is periovulatory	Yes, if patient has ovarian-type stroma in testis
Prolactin level, 6.4 ng/ml (normal)	Yes	Yes
Thyrotropin level, 1.42 $\mu$ IU/ml (normal)	Yes	Yes
Thyroxine level, 1.3 ng/dl (normal)	Yes	Yes
Bone mineral density T scores, -1.10, -0.20, and -0.90	Maybe; can be nutritional	Yes
Presence of adnexal cysts	Yes; müllerian remnants	Yes; müllerian remnants
Follicle-stimulating hormone levels, 1.9 IU/liter and 2.1 IU/liter (very low)	No, if patient has a relatively elevated luteinizing hormone level	Yes

was noted on the pelvic examination represented a tumor in a testis. In general, gonadal tumors that are associated with complete androgen insensitivity syndrome are germ-cell tumors (usually gonadoblastoma, dysgerminoma, or seminoma). However, Sertoli-cell adenomas and tumors of the Sertoli and Leydig cells are also common.<sup>17</sup> Magnetic resonance imaging (MRI) would be helpful in confirming the presence of testes and evaluating for an associated tumor in this patient.

*Dr. Virginia M. Pierce (Pathology):* Dr. Sacha, what was your clinical impression when this patient was evaluated in the fertility center?

*Dr. Sacha:* During the first visit, the principal diagnostic considerations were müllerian aplasia — including müllerian aplasia with premature ovarian insufficiency or with 46,XX gonadal dysgenesis — as well as complete androgen insensitivity syndrome. Several days later, the anti-müllerian hormone level was found to be mark-

edly elevated (579 ng per milliliter; reference range, 0.9 to 9.5), and the results of the chromosome analysis revealed a 46,XY karyotype. These results were consistent with the diagnosis of complete androgen insensitivity syndrome. At this time, additional laboratory tests were performed; the total testosterone level was markedly elevated (877 ng per deciliter; reference range for women, <50), as were the levels of dehydroepiandrosterone sulfate (692  $\mu$ g per deciliter; reference range, 31 to 228) and inhibin B (496 pg per milliliter; reference range, <139 in premenopausal women during the follicular phase, <92 in premenopausal women during the luteal phase, and <10 in postmenopausal women). As the next step in the evaluation, MRI of the pelvis was performed.

#### CLINICAL DIAGNOSIS

Complete androgen insensitivity syndrome.

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 DR. CHRISTOS COUTIFARIS'S  
 DIAGNOSIS
 

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Complete androgen insensitivity syndrome, with Sertoli-cell adenoma or another tumor with hypersecretion of inhibin B.

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 DISCUSSION OF IMAGING STUDIES
 

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*Dr. Aoife Kilcoyne:* MRI of the pelvis, performed before and after the administration of contrast material (Fig. 2), revealed a vagina that was normal in length. No discernible uterus or cervix was identified. Cordlike structures, which were best seen on the contrast-enhanced images, extended from the superior aspect of the vagina to the right and left inguinal canals, following the expected course of the round ligaments of the uterus. These structures became symmetrically dilated near the deep inguinal ring. On T<sub>2</sub>-weighted imaging, there were bilateral thin, linear, hyperintense tubelike structures along the course of the round ligaments. These structures most likely represented isthmic and interstitial segments of the fallopian tubes or lymphatic vessels. Right and left gonads were identified in the anterior pelvis, alongside the tubelike structures. No definite follicles were seen. Some gonadal tissue followed the course of the round ligaments into the inguinal canals. There were no gonadal masses.

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 DISCUSSION OF UROLOGIC  
 MANAGEMENT
 

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*Dr. Adam S. Feldman:* The patient was referred to the urology clinic for management of intraabdominal gonads. She asked that we remain vague in our discussions with her husband regarding the purpose of her clinic visit. She also expressed a strong preference that we refer to the gonads only as such and that we not use the term “testes,” which would have a male connotation. These requests highlight the potential psychological effects of the diagnosis of the androgen insensitivity syndrome on patients and their partners and family members.

Complete androgen insensitivity syndrome is most often diagnosed during childhood, when a testis is found at the time of an inguinal hernia repair, or at puberty, when a patient presents

with primary amenorrhea. Approximately 50% of patients with complete androgen insensitivity syndrome have an inguinal hernia, and 1 to 2% of female patients with an inguinal hernia have complete androgen insensitivity syndrome.<sup>18-20</sup> Any female patient who undergoes an inguinal hernia repair during childhood would usually also undergo routine vaginoscopy to confirm the presence of a cervix or undergo diagnostic laparoscopy by way of the hernia sac to rule out the presence of intraabdominal testes. This case is particularly interesting because the patient had reached adulthood without a specific diagnosis being made. Among adults with intraabdominal testes, the risk of testicular cancer (typically seminoma or gonadoblastoma) is approximately 1 to 2%.<sup>21,22</sup> In comparison, the incidence of testicular cancer in the general population is 5.7 per 100,000.<sup>23</sup> Among patients whose testes are removed before puberty, the risk of testicular cancer occurring before removal is extremely low.

Because this adult patient was at risk for occult or future development of cancer, we recommended surgical removal of the intraabdominal gonads. In contrast, among pediatric patients with complete androgen insensitivity syndrome, the optimal timing of orchiectomy can be challenging and an individualized approach is important.<sup>24</sup> The gonads produce estradiol, which contributes to the development of a female phenotype; therefore, many prefer to leave the gonads in situ until puberty is complete. Patients for whom gonadectomy would not be delayed include those with palpable testes and those with an inguinal hernia. It is also important to ensure that the patient has a diagnosis of complete, rather than partial, androgen insensitivity syndrome; in cases of partial androgen insensitivity, virilization can occur at puberty and thus earlier gonadectomy may be preferable. Finally, one must consider the need to discuss the presence of intraabdominal testes with a postpubertal female patient and the potential psychological effects of such a discussion.

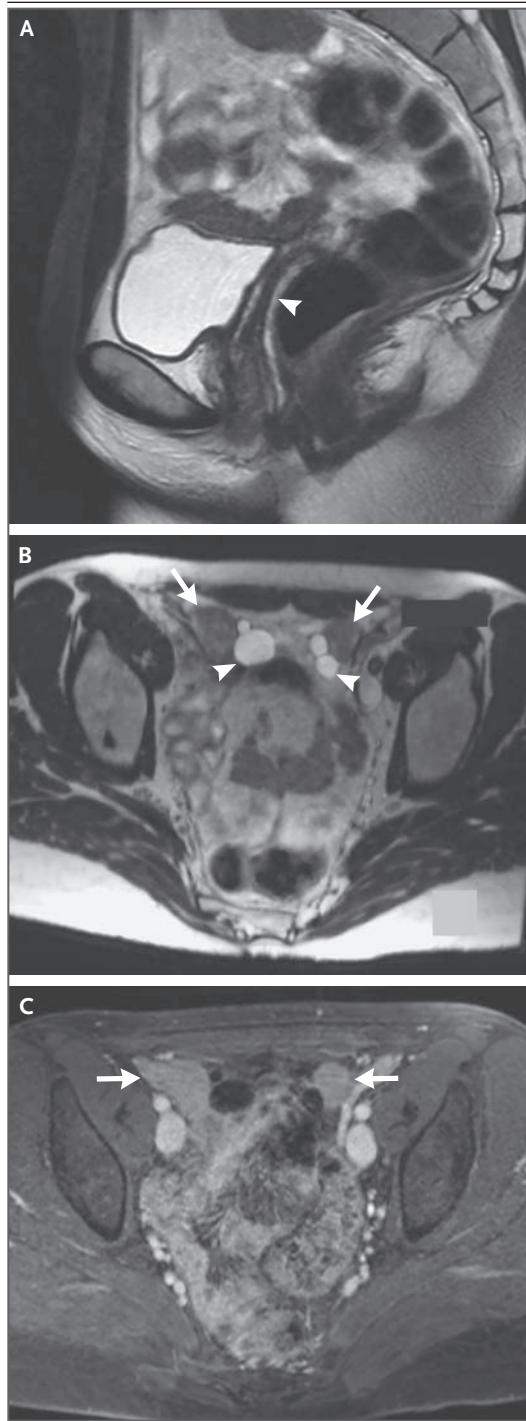
The patient underwent an uncomplicated bilateral laparoscopic orchiectomy (Video 1, available with the full text of this article at NEJM.org). Orchiectomy specimens were sent for pathological examination. After surgery, estrogen-containing hormone-replacement therapy was begun. Because the uterus was absent, no progestin was needed.



A video showing  
the orchiectomy  
is available at  
NEJM.org

**Figure 2. MRI of the Pelvis.**

A sagittal T<sub>2</sub>-weighted image (Panel A) shows a vagina that is normal in length (arrowhead). The uterus and cervix are absent. An axial T<sub>2</sub>-weighted image (Panel B) shows gonads (arrows) in the anterior pelvis, with multiple cysts (arrowheads) around the gonads. No definite follicles are shown. An axial T<sub>1</sub>-weighted, fat-saturated image, obtained after the administration of contrast material (Panel C), shows symmetric, homogeneous enhancement of both gonads (arrows).

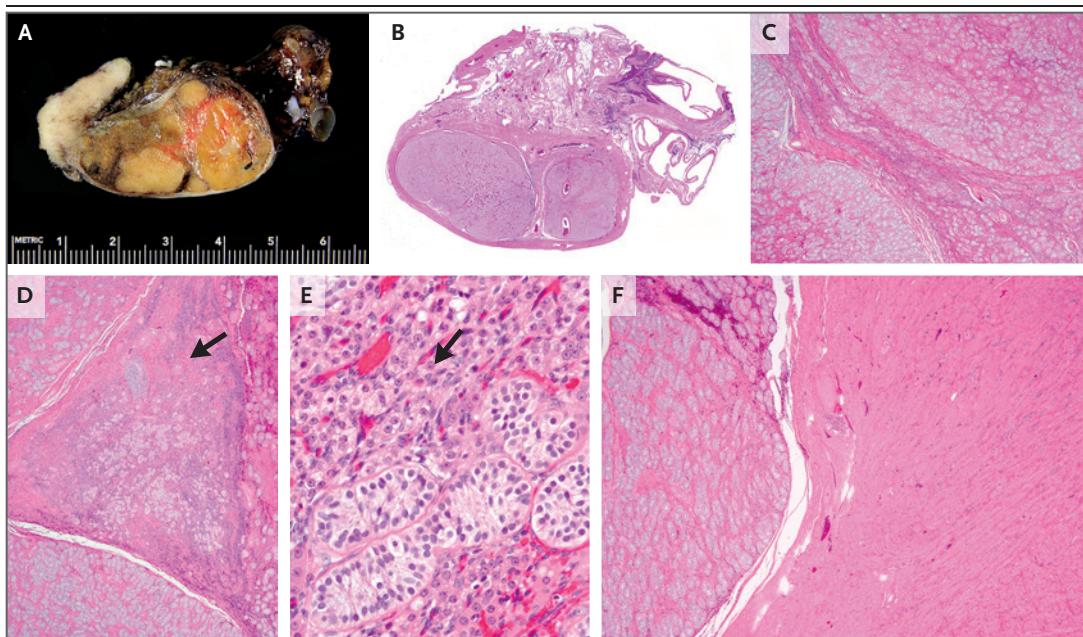


## PATHOLOGICAL DISCUSSION

*Dr. Esther Oliva:* The right testis weighed 19 g and measured 5.3 cm by 2.5 cm by 0.6 cm, and the left testis weighed 24 g and measured 4.1 cm by 2.6 cm by 2.1 cm (Fig. 3). Each testis had cystic structures in the superior portion (measuring 2.1 cm by 2.2 cm by 1.2 cm in the right testis and 1.6 cm by 1.1 cm by 1.1 cm in the left testis) and white, firm cordlike structures in the inferior portion. Sectioning of the testes revealed multiple tan nodules of various sizes within a soft, darker brown parenchyma. On microscopic examination, the most striking feature was the presence of multiple hamartomas, which were composed of small elongated, straight tubules lined by immature Sertoli cells, admixed with occasional spermatogonia. The tubules were separated by groups of Leydig cells and stroma with varied hyalinization. The Leydig cells sometimes formed small hyperplastic aggregates, whereas the ovarian-type stroma was located focally within the testicular parenchyma. Adnexal cysts, which were lined by simple cuboidal-to-columnar epithelium that was focally associated with cilia, were adjacent to primitive remnants of wolffian duct. In the paratesticular areas, marked smooth-muscle hyperplasia was present.

In patients with complete androgen insensitivity syndrome, the testes are found in an abnormal location, most often the abdomen (in approximately 80% of cases). The testes typically have three components: Sertoli-cell tubules with associated occasional spermatogonia, Leydig cells, and stroma that may be reminiscent of ovarian-type stroma. All three components were seen in this patient. These components undergo a spectrum of morphologic changes before, during, and after puberty.<sup>25,26</sup> Most striking is the development of multiple bilateral nonencapsulated

Sertoli-cell hamartomas within the testicular parenchyma after the first decade of life. Such hamartomas are often composed of Sertoli-cell tubules admixed with Leydig cells (seen in this patient), but on rare occasions, the hamartomas



**Figure 3. Orchiectomy Specimens.**

A photograph of the specimen (Panel A) shows that the testes are replaced by multiple well-defined nodules of various sizes, with a homogeneous, white-to-tannish-yellow cut surface. On hematoxylin and eosin staining (Panel B), testicular nodules and paratesticular cysts are shown. At higher magnification (Panels C through F), the nodules are composed of immature, fetal Sertoli-cell tubules within a fibromatous background (Panel C). The Sertoli-cell tubules are composed of cells with small, round, uniform nuclei and abundant pale cytoplasm (Panel D); no germ cells are shown. The tubules are surrounded by Leydig cells with larger nuclei and prominent nucleoli (Panel D, arrow) and are admixed with an ovarian-type stroma (Panel E, arrow). Evidence of smooth-muscle hyperplasia is shown at the edge of the testis (Panel F).

may be predominantly or solely composed of an ovarian-type stroma.<sup>14,27</sup>

In patients with the androgen insensitivity syndrome, sex cord–stromal tumors may develop; these are most commonly Sertoli-cell adenomas, which can be distinguished from hamartomas by the paucity or absence of Leydig cells.<sup>28</sup> In very few patients, a tumor that resembles a sex cord tumor with annular tubules may develop.<sup>29</sup> Of utmost concern is the potential for the development of malignant germ-cell tumors, most commonly seminomas. Although the risk of the development of seminoma is lower with the androgen insensitivity syndrome than with other disorders of sexual development, the risk increases over time.<sup>22,30,31</sup>

An epididymis or ductus deferens may develop in patients with the androgen insensitivity syndrome, although this is uncommon; remnants of wolffian duct are noted in approximately 25% of patients. Fallopian tubes have been reported in

up to 36% of patients.<sup>25</sup> Smooth-muscle hyperplasia (seen in this patient) may occur in the tunica albuginea of the inferior pole and in the caudal portion of the epididymis,<sup>32</sup> and thus leiomyomas may develop.<sup>17</sup> Cystic structures that are juxtaposed to the testes (also seen in this patient) may be derived from either wolffian or müllerian ducts and may become large.<sup>33,34</sup>

#### ANATOMICAL DIAGNOSIS

Prepubertal testes with multiple Sertoli-cell hamartomas, paratesticular hyperplastic muscle, and adnexal cysts, consistent with the androgen insensitivity syndrome.

#### DISCUSSION OF INFERTILITY MANAGEMENT AND FOLLOW-UP

*Dr. Mary E. Sabatini:* Because infertility is a diagnosis that involves two people, we encourage each

partner to sign a form for release of information that enables providers to share one partner's medical findings with the other partner. However, having permission to share information does not mean that everything is automatically disclosed. In this case, given the potential for distress related to the fact that the patient's chromosomal makeup was different from the gender with which she identified, the decision was made to relay all test results, including the karyotype, to the patient without her spouse present. The mechanism for the development of a female phenotype in the context of a male karyotype was explained to the patient as a mutation in the androgen receptor that makes it nonfunctional.

At initial presentation, the patient and her husband had met with a social worker because of the need for third-party reproduction with an oocyte donor and a gestational carrier, in accordance with the American Society of Reproductive Medicine guidelines.<sup>35,36</sup> The same social worker was available at the time that the karyotype was disclosed, and together, the physician and social worker addressed the psychosocial aspects of this disorder of sexual development and the implications for the patient's marriage.

Because 70% of cases of the androgen insensitivity syndrome are inherited, we also discussed that there were potential ramifications for her family, particularly her two sisters.

The patient's immediate reaction was that she would not disclose her diagnosis to her husband or family. However, she ultimately reversed this decision and told them. The patient has elected not to undergo testing to determine her specific androgen-receptor mutation. Her sisters have not yet attempted pregnancy and do not have immediate plans for family building, so they have not pursued genetic testing. The patient and her husband conceived with the use of an oocyte donor and a gestational carrier. A singleton intrauterine pregnancy is ongoing.

#### FINAL DIAGNOSIS

Complete androgen insensitivity syndrome.

This case was presented at Obstetrics and Gynecology Grand Rounds.

Dr. Sabatini reports receiving consulting fees from Confer Health. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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