46/XX CHROMOSOME CONSTITUTION OF A TRUE HERMAPHRODITE

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The influence of the Y-chromosome in sex development is apparently considerable, since testes and a male phenotype are observed in individuals who possess as many as 5 X-chromosomes in addition to the Y.[1] Since a single X-chromosome in the absence of a Y results in a female phenotype, it appears in fact that the Y-chromosome is a prerequisite for the development of human testicular tissue. The fact that the majority of true hermaphrodites (19 out of 25) have a normal female XX complex[2] is thus puzzling. It would seem that though the Y-chromosome has considerable influence in testicular differentiation, it is not the sole factor.

This report of a true hermaphrodite with an apparently normal female chromosome constitution lends further support to the theory that testicular tissue can develop in the absence of a Y-chromosome.

CASE REPORT

An African, aged 30, was admitted with a history of lower abdominal pain of acute onset. She had the appearance of a woman and had been reared as a female (Figs. 1, 2). She had never married. Menstruation commenced at the age of 15. Oligomenorrhoea was a constant feature. The external genitalia were female with separate labia majora and minora bounding a vestibule into which opened a normally situated urethra and vagina. However, certain masculine features were evident—an enlarged clitoris and a mass in the right labium majus. The skin overlying this mass was somewhat rugose.

Gynaecography and hysterosalpingography showed a bicornuate uterus. The right adnexal fold seemed to terminate in the inguinal canal.

During laparotomy it was seen that the right uterine tube extended from the right horn of a normal-sized bicornuate uterus, through the inguinal canal, into the labium majus. Here it was associated with a mass which was partially covered with a processus vaginalis and had the outward appearance of an ovary. This proved histologically to be an ovotestis (Fig. 3). It contained numerous corpora lutea, a few corpora albicantia and seminiferous tubules with marked thickening and hyalinosis of the basement membrane. The tubules were lined by Sertoli-like cells and a few spermatogonia. There was no evidence of spermatogenesis. The interstitial cells of Leydig were hyperplastic (Fig. 4).

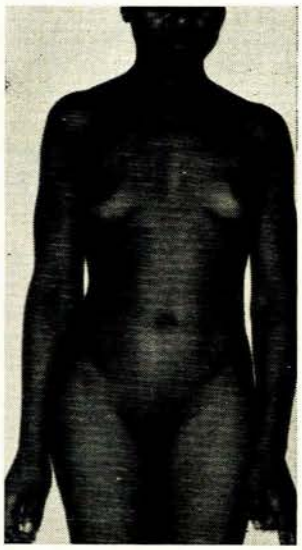

Fig. 1. Female phenotype, well-developed breasts and right scrotal mass.

The left gonad was cystic and haemorrhagic and proved histologically to consist only of ovarian tissue. The left uterine tube had undergone torsion.

Buccal and vaginal smears and the interstitial cells of the ovotestis showed a positive sex-chromatin pattern. Chromosome preparations using the method of Moorhead *et al.*,[3] were made from peripheral blood cultures (Fig. 5). Fifty technically satisfactory cells were counted (Table I).

TABLE I. DISTRIBUTION OF CELLS

No. of chromosomes	44	45	46	47
No. of cells	1	3	44	2

8 karyotypes prepared from cells with 46 chromosomes were all identical and showed a normal female pattern. The skin unfortunately could not be examined.

DISCUSSION

It appears that testicular tissue has developed here in the absence of an intact Y-chromosome but not necessarily in the absence of Y-genes. Y-chromosomal material may be present, translocated onto another chromosome, or on the X-chromosome as a result of crossing over of all or part of the homologous segment during spermatogenesis. Autosomal sex-determining genes may be involved. The evidence of the karyotype does not permit the elimination of any of these possibilities, in the present case. All that can be stated is that the Y-chromosome as such is not overtly present. Although the chromosome and sex-chromatin studies suggest the absence of mosaicism, it is conceivable that this is present but undetected.

If Y-chromosomal material is indeed absent from the complement, testicular development may have resulted from a variety of factors, including corticomedullary im-

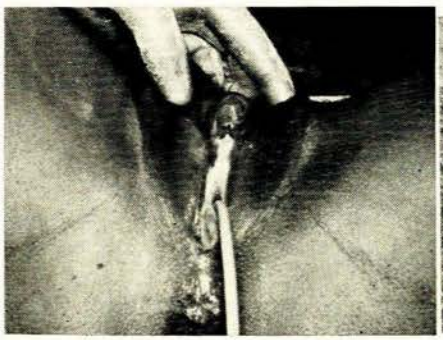

Fig. 2. External genitalia of the patient.

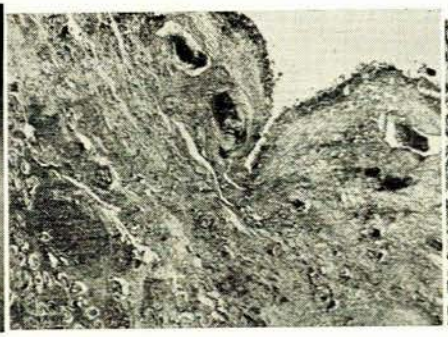

Fig. 3. Section of the ovotestis showing a portion of a corpus luteum and adjacent testicular tissue.

Fig. 4. Testicular portion of ovotestis. Interstitial cell hyperplasia is evident.

balance,[2] or abnormalities of gonial cell migration such as those demonstrated in amphibia by Witschi.[4,5] The possible development of the testicular portion from persisting medullary remnants as a result of later androgenic influences (these are discussed below), is unlikely, since it would leave the earlier manifestations of gonadal duct masculinization unexplained.

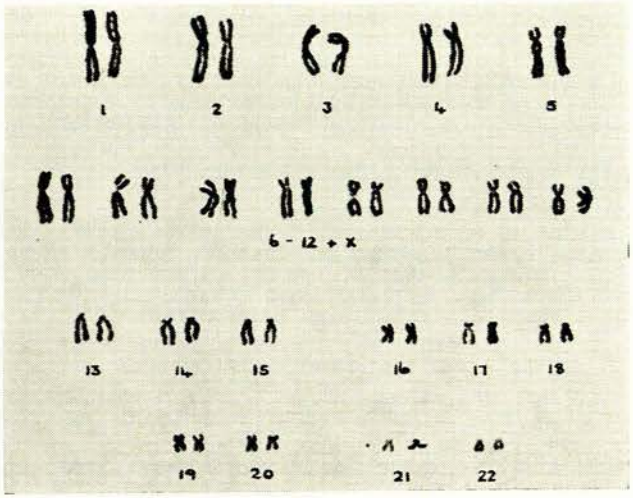

Fig. 5. Karyotype of the true hermaphrodite.

The unilateral development of the ovotestis may be explained by the known assymmetry of the human gonads,[6] or may be the consequence of a mosaic genetic state in the individual which results in an abnormal reactivity of one gonad to normal stimuli.

Testicular tissue, once formed, may affect further sexual differentiation by inducing masculinization of the ipsilateral sexual duct system.[7] However, since an almost completely female development of the ducts has occurred in this case, it might be suggested that the androgenic influence of the relatively small amount of testicular tissue present was below the threshold necessary to produce gross masculinization. Thus there is only partial inhibition of the development of the paramesonephric ducts (as indicated by the bicornuate uterus).[8] One must also assume that there is great sensitivity of the clitoris to masculinizing hormones to account for its enlargement in this case. On the other hand the androgenic influence may have been above threshold but operative at an unsuitable time.

The observed phenomena are probably most satisfactorily explained by supposing that moderately strong masculinizing influences were operative rather late in development. The earliest stage at which masculinization appears to have occurred in this case is the time of fusion of the paramesonephric ducts which is normally at about 56 mm.[9] It is probable that the androgenic potency of the testicular tissue increases at about this time—Gillmann has described an initial hyperplasia of the foetal interstitial cells which is well-developed between 50 and 140 mm.,[10] and there is evidence that the cells are functionally active at this time.[10,11] It may be supposed that the earlier differentiation of the ducts was unaffected because of subthreshold levels of masculinizing hormone present before this hyperplasia. In the normal female, involution of the mesonephric ducts occurs from 42 to 55 mm.,[10] i.e. just before the onset of maximal interstitial cell function.

Another possible source of androgens in the later embryo is the adrenal cortex. It seems that while cortical secretion alone is insufficient to produce masculinization,[12] in some situations at least it is able to maintain masculine features in castrated animals.[13] It is evident too from chemical assays, that the foetal adrenal cortex contains androgens.[14,15] That these are probably secreted is seen from the female pseudohermaphrodites produced by prenatal over-activity of the cortex. It seems that effective secretion of androgens from the adrenal occurs only relatively late in foetal development, since female pseudohermaphrodites of the adrenal variety invariably have paramesonephric duct derivatives (although the development of these may be somewhat retarded).[16]

We may conclude that although it is probable that phenomena of sexual development vary in their sensitivity to masculinizing stimuli, the partial masculinization of the genital tract observed in this case is probably due to the androgenic activity of the normally hyperplastic interstitial cells, possibly reinforced by the activity of the foetal adrenal gland.

SUMMARY

Chromosomal analysis of a true hermaphrodite with a unilateral descended ovotestis showed a normal female complement. It is suggested that the partial masculinization in this case resulted from androgenic influences after the early stages of genital tract development. The secretions of the hyperplastic interstitial cells and probably the adrenal cortex must have been responsible for, or contributed to, this masculinization.

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