Gonadal Dysgenesis in a Phenotypic Female with an XY Chromosomal Constitution

E. KAPLAN

SUMMARY
A phenotypic female with an XY karyotype and pure gonadal dysgenesis is described. Bilateral streak gonads may be found in patients with features of Turner's syndrome and also in phenotypic females without the somatic abnormalities described in Turner's syndrome. Mixed gonadal dysgenesis refers to the presence of a unilateral streak gonad and contralateral testis in a phenotypic female. Dysgenetic gonads are more liable to undergo malignant change, especially in patients with an XY karyotype, and in those with mixed gonadal dysgenesis. Laparotomy and removal of the dysgenetic gonads is indicated in patients with an XY karyotype. If a 46,XX chromosomal pattern is present, the malignant potential is probably less, but laparotomy is still indicated to enable a prognosis to be given regarding fertility.


In gonadal dysgenesis there is failure of ovarian or testicular differentiation, and gonads consist of streaks of fibrous tissue. It has usually been associated with the clinical picture of Turner's syndrome or with patients with Turner's stigmata, in which normal ovaries are replaced by thin white streaks of ovarian stroma, but it may also occur in phenotypic females without the somatic abnormalities seen in Turner's syndrome. In view of the increased possibility of malignancy developing in dysgenetic gonads, removal of the gonads is indicated in these patients. A phenotypic female with pure gonadal dysgenesis and a 46,XY chromosomal constitution is described.

CASE REPORT
A 20-year-old phenotypic Black female presented with a history of primary amenorrhoea. Breast development and growth of scanty pubic hair were noted from 15 years of age. The patient was feminine in appearance and behaviour, although her general build was eunuchoidal. Her height was 1.60 m and there was no evidence of Turner's syndrome or Turner's stigmata. Positive physical findings included sparse axillary and pubic hair, small breasts with areolae but no nipple development, and external genitalia which were fairly normal, with the labia majora marginally infantile. She was a virgin and a hypoplastic uterus was felt on rectal examination. There were no adnexal masses. X-ray films of the chest and pituitary fossa were normal. The 24-hour urine 17-ketosteroids were 9.6 mg, and 17-hydroxycorticosteroids were 14.5 mg, which are in the normal range. Samples for a pituitary gonadotrophin assay were misplaced and no result was obtainable. The plasma 17β-oestradiol was 69 pg/ml, which is a low level. The buccal smear was chromatin-negative. Chromosomal analysis of the peripheral blood leucocytes showed a 46,XY karyotype on two occasions, and quinacrine fluorescence revealed the presence of a brilliantly fluorescing Y chromosome. Laparotomy showed a poorly-developed hypoplastic uterus with thin round ligaments and bilateral hypoplastic tubes. Bilateral thin streaks of fibrous tissue were present in place of the gonads. The right fibrous streak was removed. Histology confirmed the diagnosis of gonadal dysgenesis. There was fibrosis beneath the tunica of the gonad, with areas resembling ovarian stroma. There were no primordial follicles or seminiferous tubules. Numerous clusters of hilar cells with occasional small mesonephric remnants were identified. An intravenous pyelogram was normal.

DISCUSSION
Gonadal dysgenesis has classically been associated with Turner's syndrome or with Turner's stigmata. Turner's syndrome is characterized by a 45,X0 chromosome constitution, although it also occurs in patients with a 46,XX karyotype.5,6 Gonadal dysgenesis is also found in phenotypic females without the somatic malformations seen in Turner's syndrome. If bilateral streak gonads are found at laparotomy this is referred to as pure gonadal dysgenesis.1 When a unilateral streak gonad is present, with a contralateral testis, the syndrome is known as mixed gonadal dysgenesis.5

Various chromosomal patterns are associated with pure gonadal dysgenesis, and include: 46,XY,1 46,XX,1 mosaic patterns such as X0/XX,1 X0/XXX,1 X0/XY,1 X0/XY,2 anomalous X chromosome formation,1,2,3 and mosaicism involving an anomalous X chromosome. Most patients with pure gonadal dysgenesis have a normal female or male karyotype,4 so the finding of streak gonads at laparotomy does not necessarily imply an abnormal sex chromosome complement. Whatever the chromosomal pattern, patients with pure gonadal dysgenesis are of average height or tall, with a female phenotype, although many have eunuchoidal proportions. The breasts are undeveloped or small and the axillary and pubic hair is generally sparse. The external genitalia may be infantile or fairly normal. The uterus is small and no gonads are palpable. At laparotomy 'streak' gonads are found with hypoplastic fallopian tubes and uterus. Endogenous oestrogen production may...
be present, although low in amount.4 Gonadotrophin titres are either very high or within normal limits.4 Histologically, the streak gonads do not contain any germinal elements,3 the basic structure being fibrous tissue which may simulate ovarian stroma.3 Mesonephric remnants are frequently found and groups of Leydig or hilar cells may be seen.3

Why patients with normal chromosomal patterns should develop dysgenetic gonads is poorly understood. It seems fairly well accepted that gonadal dysgenesis is of a genetic nature, but the genetic mechanism is unknown.4 The finding of a normal karyotype in most cases differentiates the aetiology of pure gonadal dysgenesis from the aetiology of dysgenetic gonads in Turner's syndrome, in which chromosomal abnormalities are present in almost all cases.4 The underdevelopment of the gonads during fetal life may be the result of either a destruction of the genital ridge or failure of the primitive germ cells to reach the genital ridge.4 In cases of pure gonadal dysgenesis with an XY karyotype failure of the testes to differentiate into functional organs results in failure to suppress development of the Müllerian ducts, and in failure to stimulate development of the Wolffian ducts and external genitalia. In consequence, female sex differentiation occurs, although the genotype is masculine, as has been shown by the embryonic castration experiments of Jost.26

According to Teter and Boczkowski11 there is an unexpectedly high risk of neoplasia developing in patients with abnormal gonadal development, especially in those with a negative sex chromatin pattern and a Y chromosome. They found that 8 of 26 patients with gonadal dysgenesis without somatic malformation had gonadal tumours. Seven patients had a 46,XY karyotype and 1 had a 45,XO/46,XY mosaicism. In only 1 patient was there a definite histological diagnosis of pure gonadal dysgenesis, and a Brenner tumour was found. Another patient had mixed gonadal dysgenesis with a gonadoblastoma. In the remaining 6 patients, tumour had destroyed the gonad, making it impossible to decide whether these were cases of pure gonadal dysgenesis or of mixed gonadal dysgenesis. Seven of the 8 patients with gonadal tumours showed some degree of masculinization as evidenced by clitoral enlargement. The patient with pure gonadal dysgenesis being unaffected. As Greenblatt et al.2 have shown, patients with mixed gonadal dysgenesis may show evidence of masculinization, so that it is possible that the masculinized patients described by Teter and Boczkowski11 were cases of mixed gonadal dysgenesis. It is understandable that in such cases the unilateral intra-abdominal testis is more prone to malignancy, but it is difficult to accept that there is an increased malignant potential in pure gonadal dysgenesis, since both gonads are mainly fibrotic without any active cellular elements. Yet, development of gonadal

blastosas in patients with an XY karyotype and pure gonadal dysgenesis has been reported.12,22 Therefore it must be accepted that all patients with dysgenetic gonads do run an increased risk of developing neoplasia in these gonads.

There are no data from South Africa on the incidence of pure gonadal dysgenesis or of Turner's syndrome. Of 3 cases of pure XY gonadal dysgenesis published in the South African Medical Journal, the ethnic origin of only 1 patient is reported.13 It is therefore not possible to comment on the prevalence of pure gonadal dysgenesis among the different ethnic groups in this country. In Europe and North America the incidence of Turner and allied syndromes is in the order of 1:2 000 live female births but no information has been published on the prevalence of pure gonadal dysgenesis (J. Grace — personal communication).

CONCLUSIONS

Phenotypic females presenting with primary amenorrhoea require full investigation to elucidate the underlying pathology. Such patients include normal females with cryptomenorrhoea, pure gonadal dysgenesis, mixed gonadal dysgenesis, and testicular feminizing syndrome. Laparotomy is required in those with a Y chromosome to exclude a unilateral testis which is prone to undergo malignant change. Removal of the gonads, when bilateral streaks are found, is probably advisable because of the possibility of malignant change. In those with a unilateral testis, removal of the testis and opposite streak gonad is mandatory. In patients with a normal 46,XX karyotype, gonadal visualization and biopsy are also required, so as to provide the patient with a correct prognosis regarding fertility and marriage.

REFERENCES