45,X/46,XY/47,XY,+21 mosaicism in a hypogonadal phenotypic male

SUMMARY A phenotypically normal male was found to have a chromosomal complement of 45,X/46,XY/47,XY,+21. This mosaic pattern has been reported only twice before. Although the patient had apparently fathered two children, he now has progressive impotence, absence of sperm in the seminal fluid, atrophic testes, almost complete absence of germ cells in testicular biopsies, high plasma LH and FSH, and a low normal testosterone. There were no physical characteristics of Turner's or Down's syndromes except for dermatoglyphic features commonly associated with the latter. These observations in this patient emphasise the value of chromosomal studies in multiple tissues in cases of mosaicism with atypical clinical features.

Sex chromosomal mosaicism is known to be associated with various abnormalities of sexual differentiation. It has been observed in sterile or fertile phenotypic males and females, in subjects with ambiguous genitalia, and in true hermaphrodites. In normal sexual organogenesis, the presence of a normal Y chromosome and its associated H-Y antigen has been regarded as the determinant for the differentiation of the ambisexual fetal gonads into testes. Further differentiation in the male depends on the testes-derived Müllerian inhibiting factor and testosterone.

Trisomy 21 has been observed in association with sex chromosomal anomalies such as in Klinefelter's syndrome, XYY syndrome, triple X syndrome, Turner's syndrome, and mosaic 45,X/47,XY,+21.

This paper reports a phenotypic male with 45,X/46,XY/47,XY,+21 mosaicism, which has been reported only twice previously but without any clinical details.9 4

Case report

The proband, a 48-year-old black male, was admitted to the Hines Veterans Administration Hospital in 1977 for evaluation of recurrent chest pain since 1973. Previous stress electrocardiogram, coronary angiography, and right and left heart catheterisation had been normal. Testicular atrophy was discovered by routine physical examination and led to cytogenetic studies.

The patient had been aware of his small testes since adolescence, but virilisation was normal. He married, considered himself to have normal libido and sexual activity, and believed that he fathered two normal male children. A transurethral resection was performed in 1975 for benign prostatic hypertrophy. The patient complained of progressive impotence over the past year. He was the third child of four sibs (two males and two females). There was no history of infants with congenital malformations or spontaneous abortions in his wife or his mother.

Physical examination showed a muscular, non-eunuchoidal, well virilised male with normal external genitalia (fig 1). The testes were 2-5 cm long...
and were of normal consistency. There was bilateral gynaecomastia. Dermatoglyphic analysis showed ten ulnar loops on the fingertips, a total finger ridge count of 110, and a sum of a-b ridge counts of 60. The left and the right palmar formulas were 5.5.5.3.13'-t'tu-Au.0/0.0.0.0.0. and 9.7.5.3.13'-t'tu-Au.0/0.0.0.0.0., respectively. A Sydney line was observed on the left palm. The remainder of the physical examination was normal without any physical signs of Turner’s or Down’s syndromes.

Pertinent endocrine data (normal values in brackets) included plasma LH greater than 50 mIU/ml (5 to 20 mIU/ml), FSH 68 mIU/ml (5 to 25 mIU/ml), testosterone 0·4 µg/100 ml (0·4 to 1·2 µg/100 ml), and normal serum prolactin and thyroxine. Semen analysis showed a volume of 0·7 ml (2·5 to 6 ml), pH 8·0, and absence of sperm (50 to 100 million). Skull x-rays were normal. Buccal smears showed no Barr bodies. Testicular biopsies showed atrophy with decreased numbers of seminiferous tubules which were small, consisting mainly of Sertoli cells. There was almost complete absence of germ cells which showed no evidence of maturation. A thickened, hyalinised tunica propria and focal areas of Leydig cell hyperplasia were also observed. Psychological testing of this anxious patient indicated normal intellectual function (Wechsler Adult Intelligence Scale).

CYTOGENETIC STUDIES
Chromosome studies in peripheral lymphocytes, fibroblasts from a skin biopsy, and testicular tissues were performed using standard techniques. Accurate identification of chromosomes and differentiation of chromosome number 21 from the Y were achieved by G banding,5 C banding,6 and Q banding.7 The table shows the proportions of 45,X, 46,XY, and 47,XY,+21 metaphases in the various tissues studied. While 45,X metaphases predominated in lymphocyte cultures, the majority of metaphases contained 46,XY in the skin and testicular tissues. Trisomy 21 was found in only 5% of the metaphases in the lymphocytes (fig 2, 3).

Discussion
Court-Brown et al8 found an increase in the proportion of 45,X cells with age in males and females. The increase of 45,X cells is apparent in females after the age of 55 years and in males after 65. Approximately 7% of the cells in blood cultures of females and 1 to 2% of the cells of males may contain a 45,X complement. It appears improbable that age accounts for the high proportion of 45,X cells in the blood of our patient. In addition, the findings in the skin and testes are compatible with a post-fertilisation mitotic error resulting in this sex chromosomal mosaicism. The normal male phenotype in our patient is probably the result of the high proportion of 46,XY cells in the testes.

TABLE Proportion of karyotypes in various tissues studied

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Proportion of karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X</td>
<td>46,XY</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>73/100</td>
</tr>
<tr>
<td>Skin fibroblasts</td>
<td>2/30</td>
</tr>
<tr>
<td>Right testis</td>
<td>2/30</td>
</tr>
<tr>
<td>Left testis</td>
<td>4/27</td>
</tr>
</tbody>
</table>

FIG 3  G banded 47,XY,+21 karyotype.

FIG 1  G banded 45,X karyotype.
Case reports

Ferguson-Smith hypothesised that short stature and other somatic abnormalities of Turner's syndrome can be produced not only by the absence of an X chromosome or the deletion of its short arm, but also by a deletion from a Y chromosome. He suggested that the Y may carry genetic material which prevents the expression of Turner's features. The high proportion of 46,XY cells in the gonads and skin of our patient may explain the absence of physical signs of Turner's syndrome and the possibility that he is indeed the biological father of two children. The latter was unconfirmed, as both his children were unavailable for paternity studies.

The patient's intelligence was normal and this is in keeping with the low percentage of 21 trisomic cells. However, his dermatoglyphic pattern was more typical of that found in trisomy 21 than in normal subjects.

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Gonadal dysgenesis in a 46,XY female mosaic for double autosomal trisomies 8 and 21

SUMMARY

The proband was evaluated at 19 years of age because of primary amenorrhoea and, on chromosomal analysis, was found to have a 46,XY karyotype in 75% of her cells and 48,XY,+8,+21 in 25% of her cells. She appeared normal at birth and exhibited normal intellectual and physical development until puberty when secondary sexual differentiation failed. This young woman showed none of the dysmorphic features associated with either trisomy 8 or trisomy 21. Her XY gonadal dysgenesis was manifested by late developmental problems of amenorrhoea, sexual infantilism, and gonadal neoplasia.

Double autosomal trisomy is extremely rare and has invariably been associated with significant physical abnormalities and limited viability.1 XY gonadal dysgenesis is also uncommon, but it is compatible with normal longevity.2,3

We now describe a young woman who has XY gonadal dysgenesis and, in addition, is mosaic for double autosomal trisomies 8 and 21. Until the time of failure of pubertal progression, she was considered quite normal.

Case report

The patient weighed 1818 g at birth and was delivered vaginally after the onset of premature labour at 36 weeks' gestation. The prenatal course had otherwise been uneventful. At conception her mother was 27 years old and her father was 31 years old. Except for her prematurity, the patient appeared to be normal at birth and her subsequent intellectual and physical development were entirely normal until puberty. At 13 years of age she had undergone a right adnexitomy for an 18 cm malignant teratoma and at that laparotomy the uterus, fallopian tubes, and left gonad appeared normal and prepubertal.

The patient was first evaluated by us at 19 years of age because of primary amenorrhoea. She appeared to be an intelligent female with a height of 152·5 cm, arm span of 151·4 cm, weight of 39·5 kg, and she was normotensive. Breast development and axillary hair were lacking, but a few pubic hairs were present. Although the vagina, cervix, and uterus were infantile, the clitoris measured 1·5 × 0·5 cm. No adnexal

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