Case Reports

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A Patient with 45,X/46,XXq-/46,XXq-dic Karyotype

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Case Report

A girl of 18 years presented in 1967 with primary amenorrhoea. She was 145 cm in height. She had one brother 3 years older who was 175 cm high. Her mother, who had had no other pregnancies and was aged 24 years when the patient was born, was 165 cm. Her father, 3 years older than her mother, was dead and was said to have been about the same height as his wife. Her mother had had two radiographs for suspected placenta praevia during her first pregnancy, but no other *x*-ray exposures of abdomen or pelvis. The patient weighed about 7 lb at birth and no oedema or other abnormality was noted.

The patient's general body configuration was plump and feminine. She had small breasts towards the lower limit of normal and immature, rather widely spaced nipples. There were no naevi. Her hands and feet were normal with no evidence of shortening of metacarpals or metatarsals. Pubic and axillary hair were sparse but probably within normal limits. She had slight cubitus valgus, a short neck without webbing, and her hair line was not low. No cardiac abnormalities could be detected and her femoral pulses were normal. She was above average intelligence.

Pelvic examination under anaesthesia revealed rather infantile external genitalia, with no clitoral enlargement, a small vagina and a very small uterus—no larger than the cervix. No gonads could be palpated.

Chromosomal Findings. The patient's mother and brother had normal chromosomes. A buccal smear from the patient showed no Barr bodies, and she proved to be mosaic for 3 cell lines with differing sex chromosomes which were originally interpreted as 45,X/46,XY/46,XYdic. The most logical explanation of the largest of the 5 small acrocentric chromosomes (Fig. 1) seemed to be that it represented a Y chromosome and that the dicentric had originated by a break in the long arms of a Y followed by junction of the ends of the chromatids. No cells which suggested a 46,XX karyotype could be identified in either peripheral lymphocytes, skin fibroblasts, or gonadal tissue. The Table shows the proportions of cells in the three types found in various cultures.

Following the recognition that in man the long arms of the Y chromosome fluoresced if stained by quinacrine mustard (Zech, 1969) and that there was a very bright fluorescent spot in interphase nuclei in cells which contained a Y chromosome (Pearson, Bobrow, and Vosa, 1970) when preparations were stained by quinacrine dihydrochloride, further specimens of the chromosomes of peripheral lymphocytes and buccal smears from the patient and her brother were examined using these new fluorescence techniques. Buccal smears did not show the characteristic fluorescent spots of cells with a Y chromosome and neither the chromosome suspected of being a Y, or the one suspected of being a dicentric Y chromosome, showed any bright fluorescence.

The buccal smears of the patient's brother and his mitotic chromosomes, however, both showed the characteristically labelled Y chromosome.

If the acrocentric chromosome of the patient had been a Y it would have shown bright fluorescence of the long arms. If the dicentric had been a Y the length of the arms was probably sufficient to have determined some bright spotting as it would appear that the entire variation of the length of the long arms of Y chromosomes is determined by the fluorescent portion (Bobrow *et al*, in press).

It is now possible to identify all the chromosomes by the specific fluorescent banding patterns along their length. In the patient every cell could be seen to contain only one X chromosome, and normal pairs of C group chromosomes. In the cells with 5 short acrocentrics the 5th showed fluorescent bands characteristic of the short arms of an X chromosome. It

TABLE

NUMBER OF CELLS OF DIFFERENT KARYOTYPES FOUND IN CULTURES

Culture*	45 not XO or < 45	45,X	46(5SA)†	46dic	> 46
Blood 1	28	30	47	23	–
Blood 2	15	12	10	3	2
Blood 3	0	27	11	19	1
Total Blood	43	69	68	45	3
Gonad	1	79	83	46	5

* A skin culture was very unsatisfactory but no cells with dicentrics were seen.
† 5SA = 5 short acrocentrics (one presumably a deleted X).
The high proportion of aneuploid cells, particularly the monosomics, probably reflects the instability of 45 (5SA), and 46dic cell lines.

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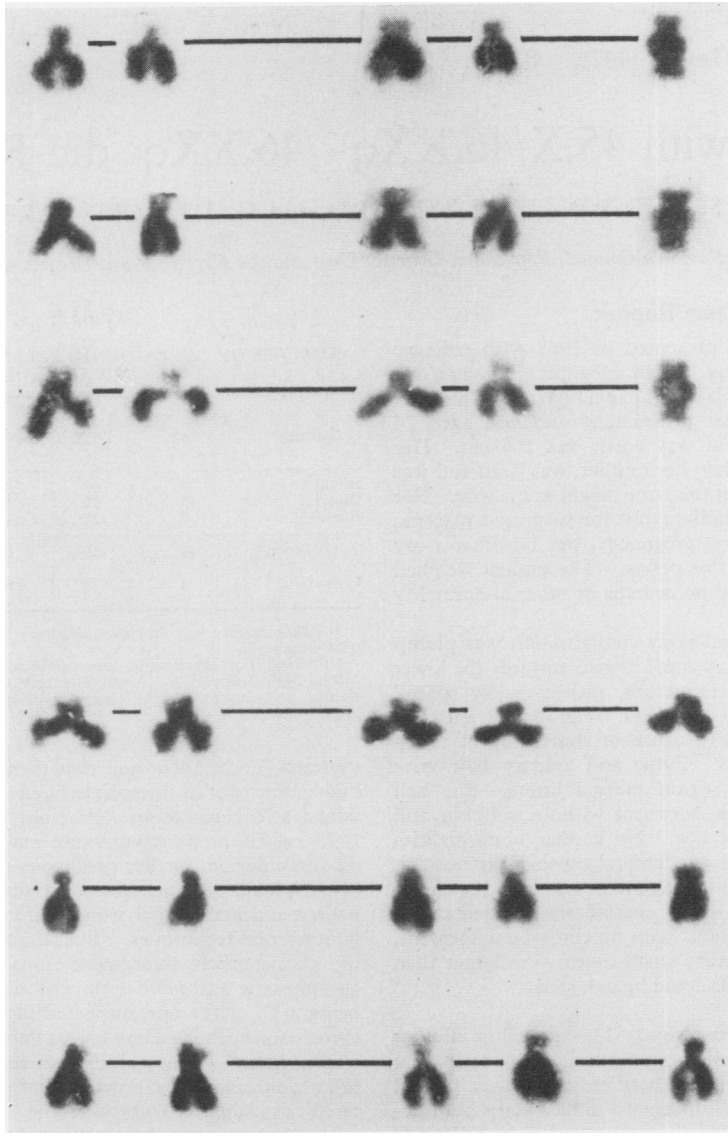

FIG. 1. The 4 short acrocentric chromosomes and one small dicentric formed from one cell line (above). The 5 short acrocentric chromosomes form the other cell line (below).

seems likely, therefore, that the chromosome initially considered to represent a Y in fact represents an X, with deletion of a large portion of the long arm, and perhaps part of the short arm. The dicentric chromosome probably was derived from such a deleted X by further deletion and reunion of chromatids. Fig. 2 shows the fluorescent karyotype of the 'C', 'G' group, and deleted X chromosome from the patient.

Dermatoglyphic Findings. Analysis of dermatoglyphs showed raised *atd* angles (R64° and L51°) and a total finger ridge count of 169 (normal females about 127).

Endocrinological Investigations. When first seen the level of urinary gonadotrophins was slightly raised—28 IU/24 hours. A 24-hour urine specimen (1960 ml) showed 17 oxosteroids, 7·6 mg/24 hours (normal 2–15), and a total 17 hydroxycorticoids 5·5 mg/24 hours (normal 4–15). Subsequently, 4 days after administration of 4500 units of pregnyl the 24-hour urine (1540 ml) values were 17 oxosteroids, 9·3 mg/24 hours,

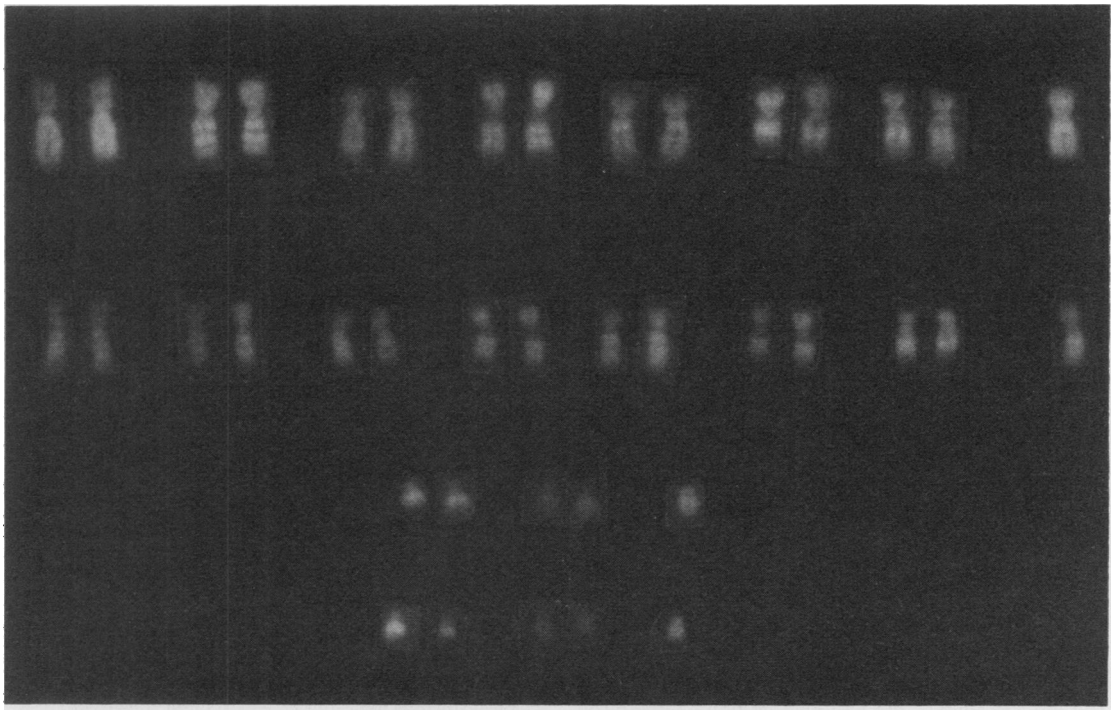

FIG. 2. Partial karyotype. The two top rows show the C group chromosomes of the patient (the one at the extreme right is the X). The bottom row shows the short acrocentric chromosomes (the one at the right has a fluorescence appearance comparable with it being derived from the short arms of the X chromosome).

and total hydroxycorticoids 5·4 mg/24 hours. Oestriol excretion was 23 μg/24 hours. These findings suggested that the patient had some gonadal tissue but gave little indication as to gonadal sex.

Findings at Laparotomy. In the light of the endocrinological and chromosomal findings it was decided that a laparotomy should be performed. The uterus was confirmed to be small but was normally formed. The Fallopian tubes were of normal size. In the broad ligament on the left side there was a slightly nodular fibrous streak, and on the right side there was a small (1·5 cm long) egg-shaped gonad embedded in fibrous tissue. The streak and the other gonad were removed and when cut both proved to have small calcified areas. Stained sections showed that there was primitive gonadal tissue not only in the presumptive gonad, but in the streak from the left side.

Histopathology. The gonad from the left side showed a thinned out layer of dense connective tissue suggestive of ovarian cortical stroma. Scattered mesonephric remnants were seen in this 'medullary area'. Inside this capsule was less cellular tissue containing many hyalinized tubular structures lined by columnar epithelium which showed eosinophilic staining suggestive of Leydig cells. Many of these showed central calcification. At the junction of the 'medulla' and 'cortex' there were several large nests of interstitial cells. A nodule from the fibrous streak in the right broad ligament showed essentially similar features.

Such findings are difficult to interpret but on the whole indicate a gonad where differentiation has not definitely proceeded to pre-testis or pre-ovary.

Discussion

It is well known that the majority of patients who have a mosaicism which includes an 45,X cell line are phenotypic females who show some features of Turner's syndrome but on the whole the clinical pictures are very pleomorphic. When, as seemed likely on grounds of chromosome morphology, it was thought that the proposita had a considerable proportion of XY and XY dic cells it seemed odd that there were no signs in the least suggestive of masculinization.

Although her brother's Y chromosome was compared with the chromosome suspected of being a Y in the patient, they seemed sufficiently similar not to make us doubt the initial hypothesis. Perhaps, with hindsight, we should have noted differences. However, the acridine fluorescence technique has clarified the situation.

Angell, Giannelli, and Polani (1970) record 3 patients with ovarian dysgenesis. All were of short stature, showed some stigmata of Turner's syndrome and had no signs of masculinization. All were chromatin negative and each was mosaic for a 45,X cell line and another interpreted as 46 chromosomes with a dicentric Y. Laparotomy in two patients showed only 'streaks' in one and 'a single sterile testicular tubule' in one gonad of the other. The authors considered that analysis of the autoradiographic finding in one of the patients was consistent with the dicentric chromosome being derived from a Y, but felt that the findings were not conclusive.

German (1970) reports briefly in a review of his experience of patients with abnormal sex chromosomes two other patients who have similar mosaicisms interpreted as 45,X/XY/XY dic. The first (his patient no. 5) was a woman 145 cm tall, who had 'a 4 cm penis like phallus but otherwise infantile female external and internal genitalia'. Her 'intra-abdominal gonads consisted partly of dysgenetic testicular and partly of unidentifiable tissue'. She had facial hirsutes, a low hair line, frontal baldness, and short false metacarpals.

German's second patient (no. 6) presented as a 149 cm-tall man. He had a short penis with hypospadias and a small 'pseudo-vaginal' opening. Laparotomy revealed uterus tubes on the right side, a testis 'adjoining a gonadal streak' and a gonadoblastoma on the left side. The presumptive Y chromosomes of the cell lines from these patients have not been examined using fluorescent techniques (J. German, personal communication).

The patient reported here is of intrinsic clinical and histopathological interest and underlines the need for positive identification of unusual sex chromosomes by modern fluorescence techniques.

Summary

Investigations are described of a girl of 18 years of age who presented with primary amenorrhoea. Endocrine investigations indicated the presence of active gonadal tissue and chromosomal findings initially suggested a mosaic 45,X/XY/XY (dic) karyotype. Fluorescent techniques indicate that the two latter cell lines did not include Y chromosomes.

The histopathology of the gonads is described and discussed.

We are indebted to our colleagues Mr G. Clarke for some of the early cytological work, and to Dr P. Pearson for the fluorescence analysis.

References

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