Mixed Gonadal Dysgenesis in Triple Mosaicism with Non-Fluorescent Y Chromosome

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(Received November 25, 1974)

An entity of gonadal dysgenesis having asymmetrical development of the gonads, a testis on one side with an undifferentiated gonad on the other, was first given the name of mixed gonadal dysgenesis (MGD) by Sohval (1963).

Several instances associated with MGD have been reported to have sex chromosome abnormalities. Most of these patients reveals X/XY mosaicism, and some of them have a structural aberration of the Y chromosome.

This report describes a male infant with a non-fluorescent Y chromosome in triple mosaicism not previously reported in MGD.

CASE REPORT

Clinical findings: A 16-month-old male infant was referred to our clinic for ambiguous genitalia. The proband was the product of a normal pregnancy and delivery, weighing 2,300g at birth, from a mother and a father aged 24 and 26 years, respectively, at his birth. On examination, external genitalia were recognized as a penis-like phallus without orifice with the presence of a urogenital sinus. Bifid scrotum contained no testicular element, but there were bilateral inguinal hernias (Fig. 1). He had no other major malformation.

Cytogenetic findings: The X- and Y-chromatin were negative in buccal mucosa cells and peripheral lymphocytes, while the Y-chromatin was positive in his father.

Chromosome analyses were performed on both peripheral lymphocyte and gonadal tissue cultures. In blood samples three cell lines were noted, consisting of a 45-cell line (16.2%) with a missing chromosome in the G-Y group; a 46-cell line (35.8%) with an apparently normal chromosome constitution; and a 47-cell line (43.6%) with a small extra acrocentric

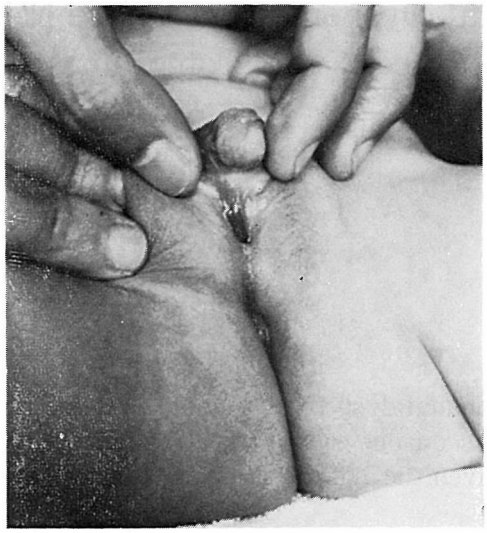

Fig. 1. Appearance of the external genitalia.

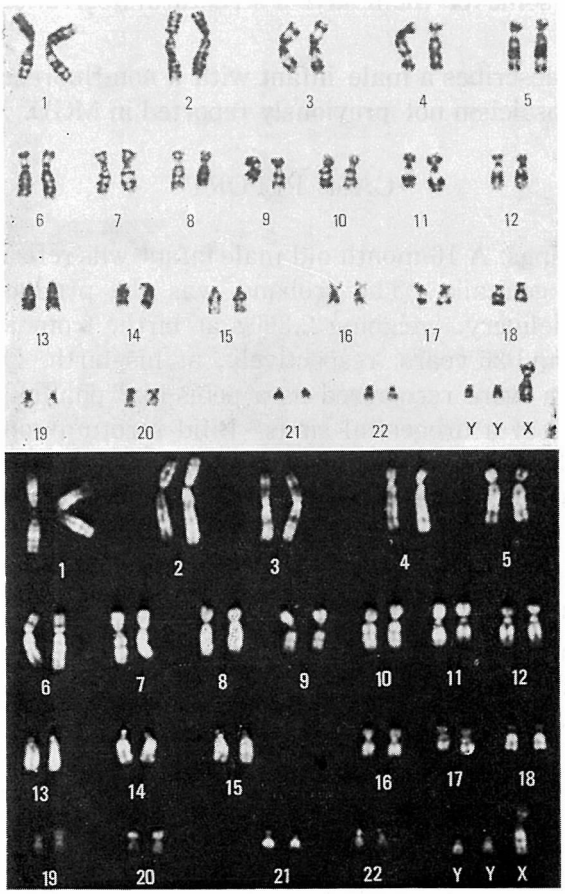

Fig. 2. G-banding (top) and Q-banding (bottom) karyotypes from 47, XYq−Yq− cell line (peripheral blood culture).

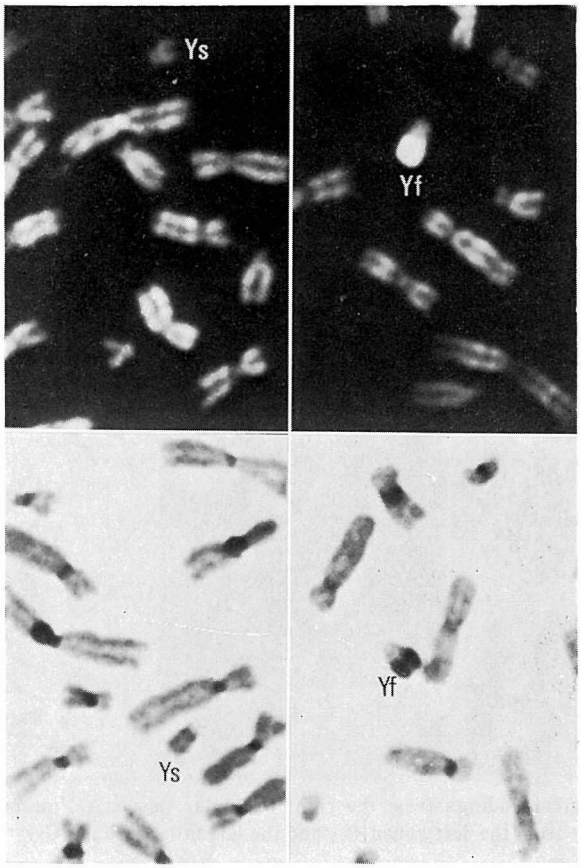

Fig. 3. Q-banding (top) and C-banding (bottom) partial metaphase plates from the patient and his father. Ys; the patient's Y, Yf; the father's Y.

chromosome.

The following banding procedures were applied in order to identify the missing and extra chromosomes. G-banding (Seabright, 1971) karyotype revealed that the extra small acrocentric chromosome had a faint band on the long arm (Fig. 2). Q-banding (Caspersson *et al.* 1970) failed to demonstrate the Y chromosome having a characteristic bright fluorescent band (Fig. 2). The extra acrocentric chromosome had a faint fluorescent band on the proximal segment of the long arm. All the other chromosomes showed normal fluorescent patterns. The long arm of the Y chromosome of the father had a brilliant portion (Fig. 3). C-banding (Sumner, 1972) method was performed on the chromosomes of the patient and his father. The Y chromosome of the father had constitutive heterochromatin in accordance with the brilliant quinacrine fluorescent part. No such heterochromatic

region, however, was noted in the proband's extra chromosome (Fig. 3).

From the results of the differential staining methods mentioned above the extra acrocentric chromosome was identified as a Y chromosome with a deleted heterochromatic or fluorescent segment of the long arm. Therefore, the chromosome constitution of the patient was interpreted as a 45, X/46,XYq− /47,XYq−Yq− in triple mosaicism.

The length of the Y chromosome relative to No. 14 was 0.605 in the patient, while 0.815 in the father. The ratio of euchromatic region of the Y

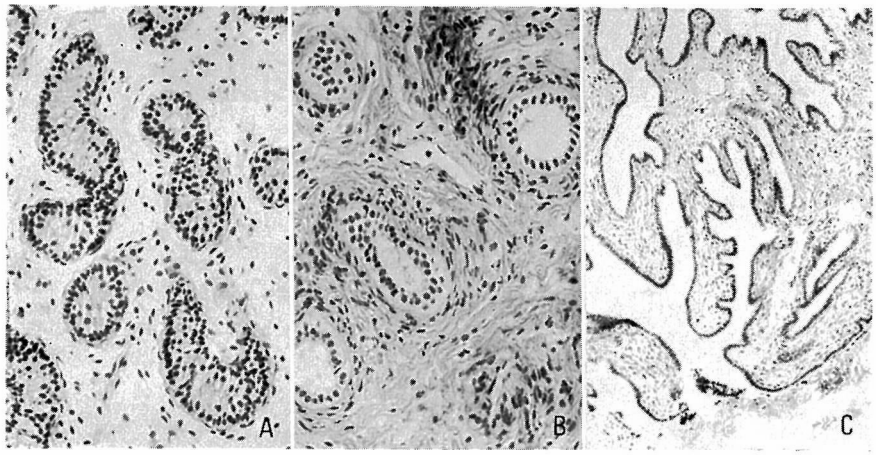

Fig. 4. Histological findings from the right testicular tissue (A), mesonephric remnant from the left gonad (B), and the left fallopian tube (C).

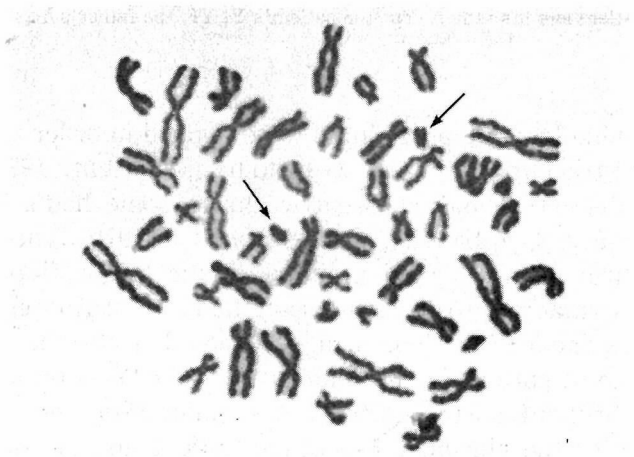

Fig. 5. A metaphase plate with a 47, XYq−Yq− chromosome constitution from cultured gonadal tissue. Arrows indicate deleted Y chromosomes.

to its whole length calculated in C-banded specimens of the father was 0.432.

Gonadal findings: Gonadal biopsies were performed during laparotomy. The right gonad showed abdominal infantile testicular tissue with numerous seminiferous tubules, which contained only undifferentiated cells suggestive of Sertoli cells. The left gonad could not be clearly identified, but a presumptive mesonephric remnant was seen (Fig. 4). There were a fallopian tube on the left side and an infantile uterus. Chromosome constitution from the right gonad revealed a 45,X/47,XYq−Yq− mosaicism; the Y chromosome was deleted and non-fluorescent (Fig. 5).

DISCUSSION

The human Y chromosome has a brightly quinacrine fluorescent portion on the long arm (Zech, 1969) and is usually transmitted unchanged from the father to his son (McKenzie *et al.* 1972). Non-fluorescent Y chromosomes demonstrate no quinacrine fluorescent segment on the distal half of the long arm. These Y chromosomes, however, are not so common in normal subjects (Borgaonkar, 1971; Schwinger, 1973).

MGD is an entity of hermaphroditism associated with asymmetrical development of gonads (Sohval, 1963). Individuals with MGD appear to represent the commonest expression of an X/XY sex chromosome mosaicism (Sohval, 1964; Davidoff and Federman, 1973). Structural abnormality, especially the long arm deletion, of the Y chromosome detected in MGD has been reported (Klevit *et al.* 1963; Takayasu *et al.* 1970; Khudr *et al.* 1973).

Subjects with an X/XY mosaicism and non-fluorescent Y chromosome have been described by several authors. Caspersson *et al.* (1971) reported four patients with a non-fluorescent Y mosaicism. Three of them revealed gonadal dysgenesis with germinal cell aplasia of testes or bilateral streak gonads, but there was no evidence of MGD. A similar case was described by LoCurto *et al.* (1972). Surana *et al.* (1973) reported an X/XYq− patient with multiple congenital anomalies, who had normal external genitalia except for a unilateral undescended testis. Bengtsson *et al.* (1974) reported male pseudohermaphrodites with an X/XYq− in a pair of monozygotic twins, which had almost identical chromosome mosaicism. The development of their gonads, however, was not identical.

MGD with an X/XYq− mosaicism was first reported in a phenotypic female by Conen *et al.* (1961). In this case the structurally abnormal Y chromosome was recognized as a very small metacentric element. Recently, Khudr *et al.* (1973) described two cases with an X/XYq− mosaicism having

a non-fluorescent Y chromosome. A female patient was to have ambiguous genitalia and asymmetrical development of gonads with characteristics of MGD. Another phenotypic male patient, however, had no major anomaly in the external genitalia, but his gonadal finding was not registered. Cases without "major" anomaly, except infantile, of the external genitalia in X/XYq− mosaicism have also been reported (Takayasu *et al.* 1970; Caspersson *et al.* 1971; LoCurto *et al.* 1972).

To my knowledge, an X/XYq−/XYq−Yq− sex chromosome mosaicism with MGD has not been reported in the literature. In the present case, the most likely explanation of abnormal findings of the external and internal genitalia may be sex chromosome mosaicism rather than structural aberration of the Y chromosome. The structural abnormality of the Y chromosome is responsible for the sex chromosome mosaicism due to non-disjunction of anaphase lagging of the affected Y chromosome, and the sex chromosome mosaicism may be responsible for MGD. Caspersson *et al.* (1971) suggested that the non-fluorescent Y chromosome was not a simple deletion of the fluorescent segment, and an unbalanced translocation should be considered.

Hsu *et al.* (1974) described a 45,X/46,XY mosaicism with a non-fluorescent Y in Turner's syndrome. In this case the Y chromosome of the patient was not shorter than that of father's Y, and they hypothesized that an altered Y may be predisposed to anaphase lag or mitotic non-disjunction leading to mosaicism. The abnormal Y chromosome may reflect an altered DNA-protein interaction due to either a changed protein or DNA configuration.

SUMMARY

A 16-month-old male infant with ambiguous genitalia is reported. Karyotype of the patient revealed a 45,X/46,XYq−/47,XYq−Yq− mosaicism in blood and 45,X/47,XYq−Yq− in gonadal tissue. The deleted Y chromosome had no brightly fluorescent or heterochromatic segment on the long arm. The father of the proband, however, had a normal fluorescent and heterochromatic region on the long arm of the Y chromosome. Gonadal tissues were characteristic of mixed gonadal dysgenesis.

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