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Dicentric Y chromosome in mixed gonadal dysgenesis

Summary. A 15-year-old girl was investigated because of ambiguous genitalia. Her chromosome studies showed a 45,X/45,Xdic(Yq) mosaicism. The identity of the dicentric Y chromosome was demonstrated by its typical fluorescent banding patterns. Histological evidence of mixed gonadal dysgenesis with intragonadal tumour was observed, confirming the occurrence of gonadoblastoma associated with mosaicism in which at least one cell line bears a Y chromosome.

A recent review by Davidoff and Federman (1973) has put into clear perspective the findings of abnormal sex development in individuals with a differentiated gonad on one side, alone or associated with a streak gonad on the other. While mixed gonadal dysgenesis has been reported fewer than 70 times in the literature, the association of this syndrome to dicentric Y chromosomes appears to be documented in only six patients (Cohen *et al*, 1973).

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Case report

The patient, a 15-year-old girl, was admitted to the Pediatric Service for evaluation of ambiguous genitalia. She was born in the Colombian countryside and although abnormal genitalia were noted at birth, she was not seen by a physician until the age of 9. No investigation or treatment of her disorder was undertaken. Details of the pregnancy, delivery, and early development are not available. The patient has three sisters and three brothers, apparently healthy. She was reared as a female but shortly before her 15th birthday, because of repeated comments by her sisters concerning her unusual genitalia, she asked for medical advice in Bogota.

Physical examination revealed a small, talkative, apparent female with a height of 134 cm and a weight of 47 kg. There was discrete temporal recession of the hairline but facial hair was absent. The palate was high arched. There was no evidence of breast development and the nipples were asymmetric. She had a mild pectus excavatum. No murmurs were heard on auscultation of the heart and the peripheral pulses were full and equal. The neck was not webbed and the thyroid was not enlarged. The upper extremities showed no cubitus valgus. The genitalia exhibited scant pubic hair and a phallus measuring 5 cm partially covered by a foreskin and with a blind urinary meatus (Fig. 1). A small introitus and vagina were easily seen. Through an infantile speculum a cervix was visualized. The remainder of the examination was unremarkable.

The X chromatin on a buccal smear was negative. On a 24-hour urine collection the 17 ketosteroids measured 4.1 mg/24h (14.2 μmol/24h); the 17 hydroxysteroids 3.5

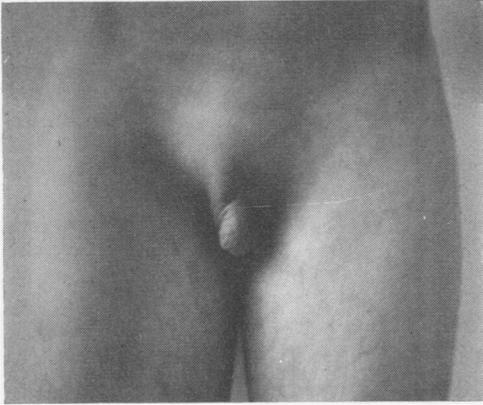


FIG. 1. External genitalia of the proband showing the enlarged phallus.

mg/24h ($12.2 \mu\text{mol}/24\text{h}$), and the pregnanetriol 1 mg/24h ($2.97 \mu\text{mol}/24\text{h}$). Bioassay for urinary gonadotropins did not show any activity. Bone age was 12 years and the fourth metacarpal bones were short. An intravenous pyelogram revealed a horse-shoe kidney.

An exploratory laparotomy revealed an infantile uterus and bilateral fallopian tubes. A streak gonad was identified on the left side and an undifferentiated gonadal structure on the right. They were both surgically re-

moved. Cyclic oestrogen therapy brought about breast development and menstrual flow 3 months later.

Microscopic examination of the surgical material revealed fibrous condensation with the typical appearance of a streak gonad on the left side. The right gonad showed a testis with severe alterations. The germinal line was absent and only few Sertoli cells were seen. The basal membrane was thickened and the Leydig cells were hyperplastic. A microscopic gonadoblastoma was identified in the testicular tissue (Fig. 2).

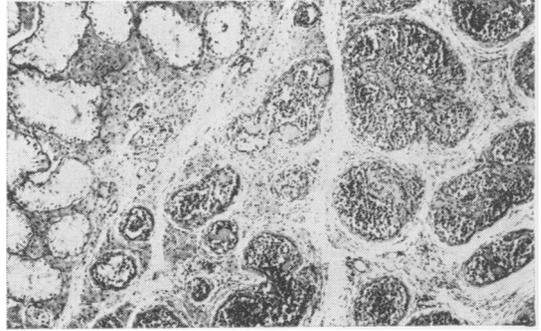


FIG. 2. Microscopic view of the right gonad showing on the left side atrophic tubules with absent germinal line and on the right, the increased cellularity of a gonadoblastoma.

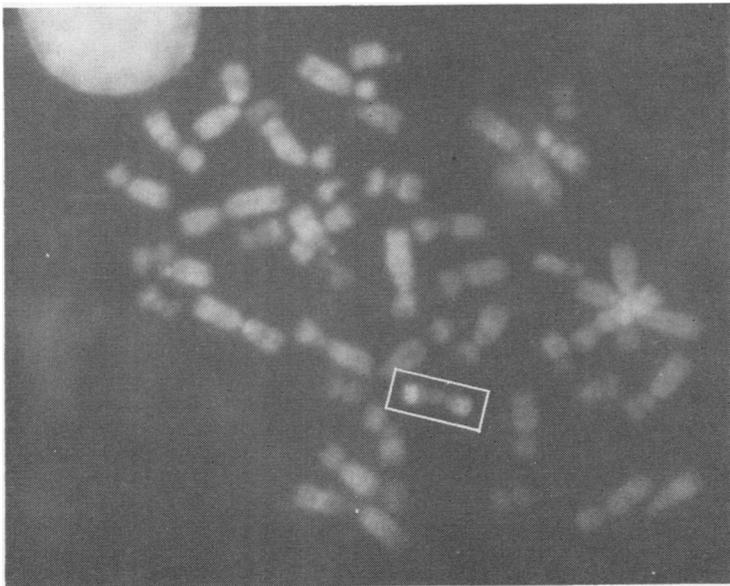


FIG. 3. Karyotype showing in the white box the dicentric Y chromosome identified by its centromeres and brightly fluorescent distal areas.

Chromosome studies

Chromosome studies were carried out in leucocytes following usual techniques. Chromosome fluorescent preparations were done following the technique described by Caspersson *et al* (1970). Smears were stained with quinacrine mustard 0.5 g for 10 min, mounted with phosphate buffer at pH 7.0 and after sealing, observed under a Zeiss photomicroscope provided with an 'HPO Lamp, an exciter filter BG 12, and barrier filters 53/54'; the photographs were obtained with Kodak panatomic X film. The smears were utilized to study interphase lymphocyte nuclei. Of 100 leucocytes studied, 30% showed a 45,X constitution while the rest exhibited a 46,Xdic(Yq) cell line. The abnormal chromosome was identified as a dicentric Y by the presence of two centromeres and the characteristic brightly distal fluorescent areas (Fig. 3).

The absence and presence of fluorescent bodies in interphase lymphocytes were recorded in similar proportions to those from metaphases. The fluorescent body appeared in some cases as a large body, but frequently was seen as a double formation (Fig. 4). This is interpreted as related to the position of the dicentric Y in resting cells.

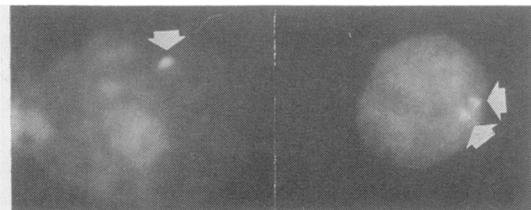


FIG. 4. Fluorescent bodies in interphase lymphocytes shown as a large body or as a double formation (arrows).

Discussion

Mixed gonadal dysgenesis has been diagnosed at all ages and the variability of the phenotypic presentation and gonadal findings depends to a large degree on the chromosomal pattern found in cytogenetic studies. An enlarged phallus which is usually, if not always, a hypertrophic clitoris constitutes the earlier clinical sign leading a clinician to refer a child for investigation of ambiguous genitalia. When a vaginal opening is present, as it occurs in about 90% of the reported cases, the index of suspicion for this diagnosis is highly increased.

The gonadal constitution in over 50% of the reported cases has shown testis plus streak, unilateral testis only, or a streak gonad plus tumour. Cytogenetically, all mixed gonadal dysgenesis patients

are chromatin negative. The most common chromosomal pattern is X/XY mosaicism. Reported mosaics with Y chromosome abnormalities, include isochromosome, translocation, double Y, triple Y, and deleted Y—all reviewed in the work of Davidoff and Federman (1973). Although these authors suggest that individuals with gonadal tumours may constitute a different group from the classic mixed gonadal dysgenesis patient, our case follows more the characteristics of the latter. In effect, she is short, lacks breast development, and her appearance as well as the radiological findings suggest, if anything, Turner's syndrome. Furthermore, our patient confirms past reports that gonadoblastoma is always associated with the presence of a cell line bearing a Y chromosome (Teter and Boczkowski, 1967). Desjeux *et al* (1969) have found a 20% incidence of this tumour associated with the presence of X/XY karyotypes. On this basis, we believe that in mixed gonadal dysgenesis, gonadectomy during initial laparotomy is warranted, since normal pubertal changes or additional height may not occur when adolescence arrives.

A review of the literature on the 16 reported cases of human dicentric Y chromosomes (Cohen *et al*, 1973) summarizes the possible mechanisms leading to the formation of this chromosomal abnormality and points out the wide phenotypic variability of its expression.

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