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Fetal 45,X/46,XY Mosaicism, Cytogenetic and Morphologic Findings in Pregnancy

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45,X/46,XY mosaic patients exhibit a wide phenotypic spectrum, ranging from normal females and females with Turner syndrome and normal males with mild hypospadias, to male or female pseudohermaphroditism (1). Prenatally diagnosed cases of 45,X/46,XY mosaicism represent an unbiased group. In over 90% of this group a normal male phenotype has been found. However, the postnatal diagnosis group is most probably biased by ascertainment because usually, phenotypically abnormal individuals are referred for cytogenetic studies (2,3). This case report describes a rare instance of 45,X/46,XY mosaicism in which the 45,XO karyotype was diagnosed prenatally by amniocentesis. After termination of the pregnancy, chromosomal analysis of the fetal cutaneous biopsy material and fetal cord blood cells revealed the mosaic karyotype 45,X/46,XY at a ratio of 30/70.

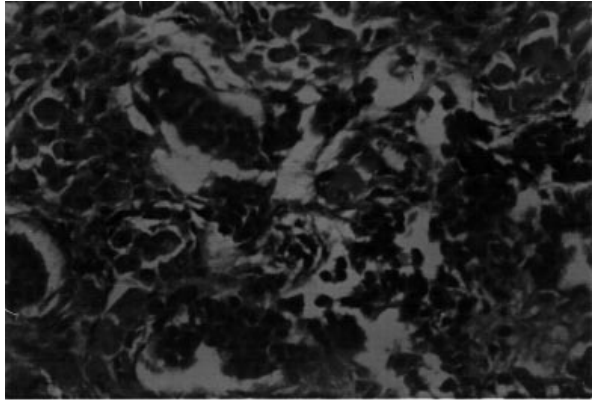
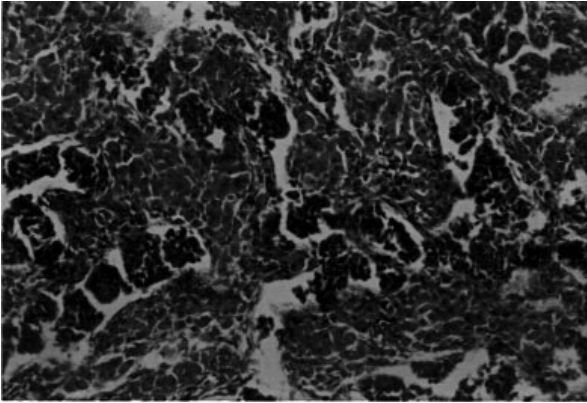
Case Report

Amniocentesis was performed in a gravida 3, para 1, abortus 1, healthy 38-year-old woman because of her advanced maternal age. She had previously given birth to a healthy girl. She was first admitted to our center at 17 weeks gestation, and amniocentesis was performed two days later. Cytogenetic analysis revealed the karyotype 45,XO in cells derived from cultured fibroblasts. The pregnancy was terminated in the 20th week of gestation. Post-mortem examination showed a fetus which was 650 g in weight and 29cm in length. The external genitalia were ambiguous. The labium major was edematous, with the appearance of a scrotum. The clitoris was prominent and there was no testicular tissue on palpation of the

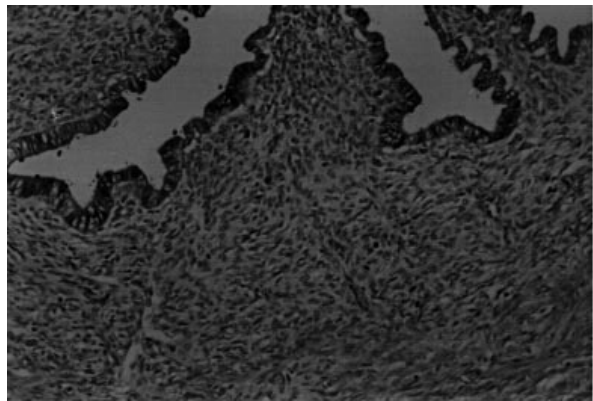
external genitalia. The autopsy revealed no macroscopic gonad or uterus in the pelvis, but microscopic examination of the pelvic tissues showed a blind uterus and a testis on the left side, while there was no gonad on the other side. Histological examination of the labia did not reveal any testicular tissue. Internal abnormalities were limited to the genital system and there was no internal malformation. Histological examination of the testis revealed immature seminiferous tubules (Figure 1a) and hyperplastic Leydig cells (Figure 1b). Sertoli cells and spermatogonic cells were also found. There was a unicorniate and blind uterus in the pelvis (Figure 2a). Endometrial-type monolayer prismatic cells were observed a lumen and under this layer there was an endometrial stroma (Figure 2b). Microscopic examination of the external genitalia showed a prostate gland (Figure 3a) and developing penis (Figure 3b).

Chromosomal analysis carried out after termination of the pregnancy on the fetal cutaneous biopsy material and fetal cord blood cells showed the mosaic karyotype 45,X/46,XY. In order to determine the ratio of mosaicism, 200 metaphases were scored and the ratio of 45,X/46,XY was found to be 30/70.

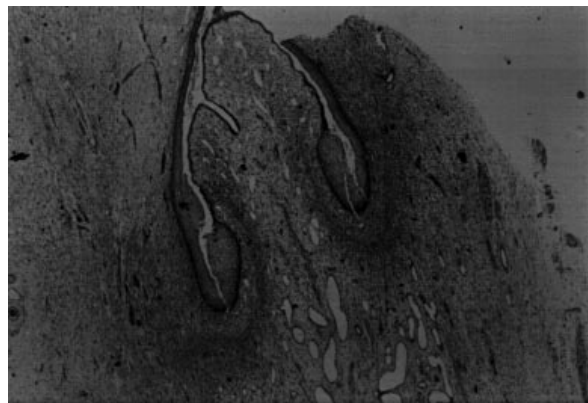
Mosaicism is defined as the presence of two or more cell lines in the same individual (4). The etiology of this mosaicism is still unclear. Mitotic non-disjunction is considered to be the cause (5). 45,X/46,XY mosaics have a wide spectrum of phenotypic appearances. Most reported cases of 45,X/46,XY individuals have female or ambiguous external genitalia with bilateral streak gonads or asymmetrical gonadal differentiation (1).



Figures 1a and 1b. Microscopic examination of the testis revealed immature seminiferous tubules and hyperplastic Leydig cells (Fig.1a. HE, X46) . (Fig.1b. HE, X230).



Figures 2a and 2b. There was a blind uterus in the pelvis (Fig. 2a. HE, X46). Endometrial type monolayer prismatic cells are lying a lumen and endometrial stroma can be seen under this layer (Fig. 2b. HE, X230).



Figures 3a and 3b. Microscopic examination of the external genitalia revealed a prostate gland (Fig. 3a. HE, X46) and developing penis (Fig. 3b. HE, X115).

Mixed gonadal dysgenesis (MGD) is a syndrome characterized by a 46,XY or a mosaic 45,X/46,XY karyotype, the presence of a testis on one side and a streak or an

absent gonad on the other, persistence of Müllerian duct structures, and a variable degree of genital ambiguity (6,7). Although most patients with MGD present ambigu-

ous genitalia at birth, a small number may exhibit normal external genitalia, often male in appearance (8). Dysgenetic gonads are morphologically and functionally abnormal. They produce an inadequate amount of testosterone, which causes incomplete masculinization of the genitals and poor development of the Wolffian duct structures. Moreover, an insufficient or delayed production of Müllerian inhibitory factor causes the persistence of Müllerian structures (8,9).

In the classical form of MGD, the testes may have a different histological appearance ranging from a rudimentary structure to a normal prepubertal gonad containing spermatogonia. After puberty these testes usually lack advanced stages of spermatogenesis. Calabrese and Valente suggested that the immature Sertoli cells are characteristic of MGD, a theory that they based on two cases. They concluded that persistent gonadotropin stimulation caused by poor production of sex steroids by the abnormal testes leads to hyperplastic-neoplastic transformation of Sertoli cells (8).

There are substantial differences between prenatally and postnatally diagnosed cases of 45,X/46,XY mosaicism. Over 90% of prenatally diagnosed cases

exhibit a normal male phenotype, whereas the postnatally diagnosed cases exhibit a wide spectrum of phenotypes (2,10). This is most probably biased by ascertainment, because only phenotypically abnormal individuals are referred for postnatal cytogenetic studies. Our case was prenatally diagnosed as the 45,XO karyotype, but the ambiguous fetal external genitalia led us to reconsider the diagnosis. Postnatal evaluation of the fetus revealed asymmetrical gonads and mosaicism.

This case demonstrates the importance of an accurate clinical evaluation of any patient independent of laboratory diagnosis. Although amniocentesis is a very reliable diagnostic method, all cases with prenatal diagnosis must be evaluated postnatally. The postnatal examination of this case showed us mixed gonadal dysgenesis, and postnatal cytogenetic analysis of cutaneous biopsy material and cord blood cells revealed 45,X/46,XY mosaicism.

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