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An Unusal Case of Hermaphroditism - A 46,XX/69,XXY Chimera

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ABSTRACT

A diploid/triploid karyotype is an uncommon but important cause of true hermaphroditism and ambiguous genitalia. Individuals have a recognisable phenotype and characteristic hydatidiform placental changes. We report a 46,XX/69,XXY chimeric hermaphrodite. This case highlights the typical features (large placenta, intrauterine growth retardation, asymmetric growth, cranio-facial anomalies, syndactyly and pigmentary dysplasia). It illustrates the importance of obtaining skin and gonadal karyotypes in the case of genital ambiguity, as the venous lymphocytic karyotype is usually diploid.

KEY WORDS

diploid/triploid karyotype, ambiguous genitalia, hydatidiform placenta

PATIENT REPORT

Our patient was the second child of unrelated Caucasian parents. An amniocentesis had been performed during an otherwise uncomplicated pregnancy because a routine 'triple test' (alpha-foetoprotein, oestriol and human chorionic gonadotrophin) to screen for Down's syndrome had suggested a high risk. The amniocentesis showed a 46,XX karyotype. The infant was born at term weighing 2.84 kg with a large, pale placenta which weighed 2.0 kg. The child had ambiguous genitalia with a small phallus and a urethral opening in the middle of bilateral labio-scrotal folds (Fig. 1). Gonads were palpable in the right labio-scrotal fold and in the left inguinal canal. Bilateral inguinal hernias were present. The child had dysmorphic features with micrognathia, macroglosia, microcephaly, a sloping forehead and wide simian crease. Chromosomal analysis on venous blood again showed a 46,XX karyotype. The blood film was suggestive of dyserythropoietic anaemia. Baseline hormone levels on day 6 (FSH <0.2 IU/l, LH <0.5 IU/l, testosterone 33.9 nmol/l, oestradiol 1,730 pmol/l) demonstrated very high levels of both testosterone and oestradiol suggesting the gonads were ovo-testes. The initial levels were presumed to be due to perinatal stimulation of the gonads and

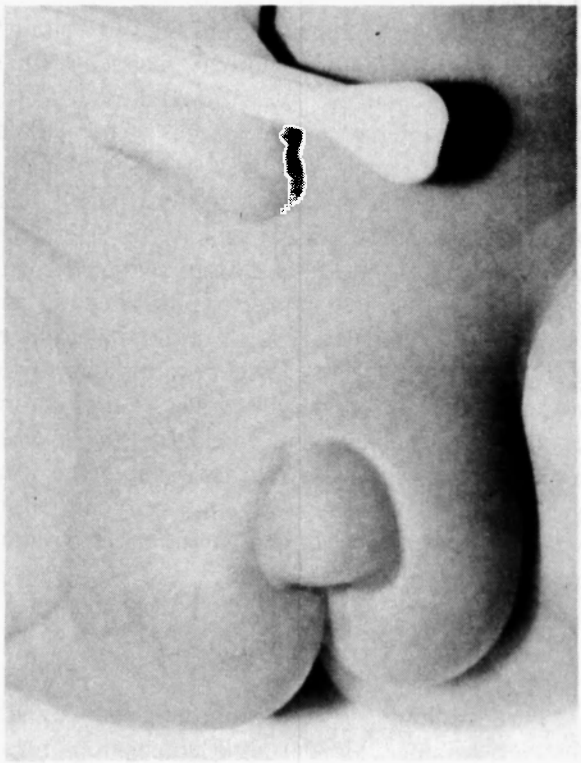

Fig. 1: Ambiguous genitalia.

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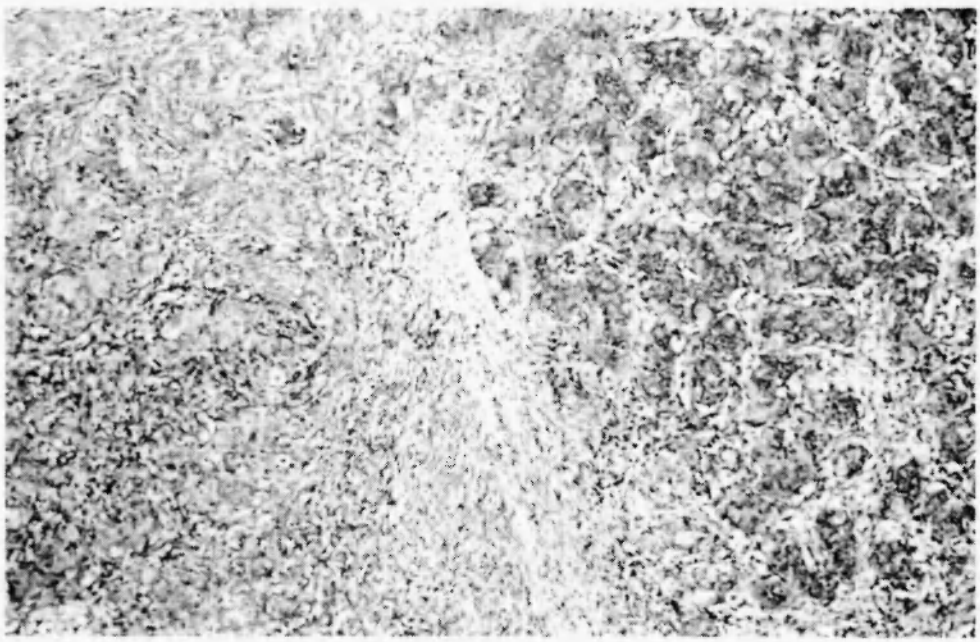

Fig. 2: Histology of gonad demonstrating appearance of ovo-testes with seminiferous cords, spermatogenic, Leydig and Sertoli cells, interspersed with primordial follicles in ovarian stroma.

subsequently fell to the levels one would expect in an infant boy.

An ultrasound and genitogram showed a straight urethra opening into a normal bladder with a utricle/vagina joining the mid-urethra with no evidence of internal female organs. After careful consideration female sex was assigned. Laparoscopy and hernia repair were subsequently performed and the gonads removed. Histology confirmed that both gonads were ovo-testes with seminiferous cords, spermatogenic, Leydig and Sertoli cells, interspersed with primordial follicles in ovarian stroma (Fig. 2). Adenexal tissue showed no evidence of Müllerian tissue. Chromosome analysis of fibroblasts and gonadal tissue revealed a diploid/triploid 46,XX/69,XXY karyotype. She subsequently underwent feminising genitoplasty with clitoral reduction and sigmoid substitution vaginoplasty.

DISCUSSION

Pure triploidy is a recognisable but usually lethal syndrome[1]. Most triploid conceptions result in spontaneous abortion although a few have been born alive but died in the neonatal period[2-4]. Triploid foetuses typically exhibit severe growth retardation, defects of the cranial bones, cleft palate, micrognathia, ocular abnormalities, low set abnormal ears, syndactyly and a simian crease[3,5,6]. Hydatidiform placental changes, genital anomalies, and haematological abnormalities such as macrocytosis and large platelets are common[1,4,7].

In contrast, individuals with diploid-triploid mosaics or chimerism rather than complete triploidy exhibit less severe phenotypic malformations and survive long term[5]. The mechanisms that give rise to diploid-triploid karyotypes (2n/3n) are complex[7]. Chimeras are the result of the aggregation of two zygotes into a single embryo, whereas mosaics derive from a single fertilised egg. The mechanism for the 46,XX/69,XXY chimerism in this patient is uncertain; cytogenetic probes were not available when this child was born. Two zygotes forming a chimera was thought to be the most likely explanation. It requires two unusual steps, e.g. double fertilisation of an ovum and its first or second polar body, or fusion of two independently fertilised ova[8]. We were unable to postulate a model whereby a diploid/triploid mosaic

with discordant sex chromosomes could be generated from a single zygote.

Diploid/triploid 46,XX/69,XXY chimeras are rare and only a handful of such cases of hermaphroditism have been reported[8,9]. Such individuals have a characteristic phenotype that they share with other diploid-triploid combinations. The presence of ambiguous genitalia appears to depend on the sex chromosome make-up. Where there is discordance of sex chromosomes, as in this child, ambiguous genitalia and hermaphroditism result[8,9]. In diploid-triploid women (46,XX/69,XXX) genital anomalies have not been noted[5,10]. In 46,XY/69,XXY mixoploidy a range of genital appearances from normal male to normal female have been described[5,11].

Identification of diploid-triploid individuals is important, as subsequent neurodevelopemental problems appear to be universal. Perhaps the most obvious clue is the extremely large and bulky placenta, which histologically exhibits hydatidiform changes. The placental changes are presumably a consequence of the triploid cell line as there are similarities with the changes seen in molar pregnancies from which triploid cell lines are frequently isolated[12]. Other characteristic phenotypic features are intrauterine growth retardation, asymmetry of the face and body (which may be present at birth or develop later with hemihypertrophy), cranial bone abnormalities, cleft palate, micrognathia, ocular abnormalities, low set abnormal ears, syndactyly and a simian crease[5,6,13,14]. Pigmentary dysplasia with both hypopigmented and hyperpigmented lesions resembling *café-au-lait* spots have been described[6,11]. Abnormal haematological indices suggesting dyserthyropoietic anaemia are also a feature[13,14].

It is important to obtain a skin or gonadal karyotype as the majority of diploid/triploid individuals have a normal diploid karyotype in venous blood[6,11,14]. As individuals with diploid/triploid cell lines usually have learning difficulties an accurate diagnosis is important for counselling and prognostic purposes.

A large bulky placenta in a child with ambiguous genitalia, intrauterine growth retardation, asymmetric growth or hemihypertrophy, syndactyly and abnormalities of the cranial and facial bones should raise the possibility of a triploid cell line and it is imperative to obtain tissue samples for a karyotype.

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