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LONG ARM DELETION OF THE X CHROMOSOME, 46,X,del(X)(q21), ASSOCIATED WITH GONADOBLASTOMA

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Summary A 28-year-old woman with short stature was found to have bilateral gonadoblastoma in the dysgenetic ovaries. Chromosome banding analysis of her cultured blood cells and skin fibroblasts revealed a terminal deletion of the long arm of the X chromosome, 46,X,del(X)(q21), as the sole karyotypic anomaly. None of the Xq− patients so far reported were associated with gonadoblastoma.

INTRODUCTION

The occurrence of gonadoblastoma has been reported almost exclusively in phenotypically female patients with gonadal dysgenesis, and such patients usually had the Y chromosome or its fragment in their somatic karyotypes (Schellhas, 1974; Hart and Burkons, 1979; Sandberg, 1980). There were also reported a few cases of gonadoblastomas which developed in the absence of the Y chromosome, showing essentially a female karyotype with or without mosaicism involving a 45,X cell line (de Bacalao and Dominguez, 1969; Salet *et al.*, 1970). To our knowledge, however, long arm deletion of the X chromosome (Xq−) has never been associated with gonadoblastoma, despite that most Xq− patients showed certain clinical features of Turner's syndrome and/or gonadal dysgenesis (Farabosco and Dallapiccola, 1974). The present communication deals with a case of gonadoblastoma associated with 46,XXq− karyotype, in whom somatic stigmata related to Turner's syndrome were not observed except for short stature.

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CASE REPORT

The patient, M.F., a 28 year-old Japanese married woman, was admitted to Hokkaido University Hospital for evaluation and treatment of gonadoblastoma in March 1977. She was born after full-term pregnancy, weighing 3.3 kg, as the second child to the healthy mother and father of 26 and 29 years with no consanguinity. The mother had no history of clinical complications, X-ray exposure and medication during the pregnancy. The patient had a normal childhood development with subsequent appearance of secondary sexual characteristics of female. The first menstration occurred at age 16 was scanty with a duration of three days. After two menstrations occurred at intervals of three months, she became amenorrhoeic, for which a hormonal therapy induced a slight but regular-cycling menstruation. At age 24, she married but never conceived, and received a regimen for ovulation induction which was not effective. Expolatory laparotomy performed at the age of 28 years revealed bilateral dysgenetic ovaries, and pathological diagnosis of gonadoblastoma was made following histological examinations of gonadal biopsies from both sides.

The histological findings indicated the characteristic architecture of gonadoblastoma, showing various rounded nests of granulosa Sertoli cells intermixed with large germ cells with vacuolated cytoplasm (Fig. 1). Calcific bodies and Call-Exner-like bodies were observed in some nests. The nests were surrounded by connective tissue in which clusters of the Leydig cells were scattered.

Table 1. Results of hormonal examinations

Hormonal level (/ml)		Plasma LH-RH test (LH-RH 100 μg iv)		
		Time (min)	LH (mIU/ml)	FSH (mIU/ml)
Plasma:				
LH	123.4 mIU	0	113.3	91.9
FSH	99.1 mIU	15	289.3	123.6
Prolactin	14.5 ng	30	358.3	145.4
Cortisol	11.2 μg	60	336.1	147.6
11 OHCS	16.9 μg	120	234.7	165.8
Estron	18.0 pg	180	193.0	137.7
Estriol	5.0 pg			
Estradiol	5.0 pg			
AFP	1.0 ng			
CEA	1.5 ng			
Urinary:				
17 OHCS	128.8 mg			
17 KS	5.8 mg			

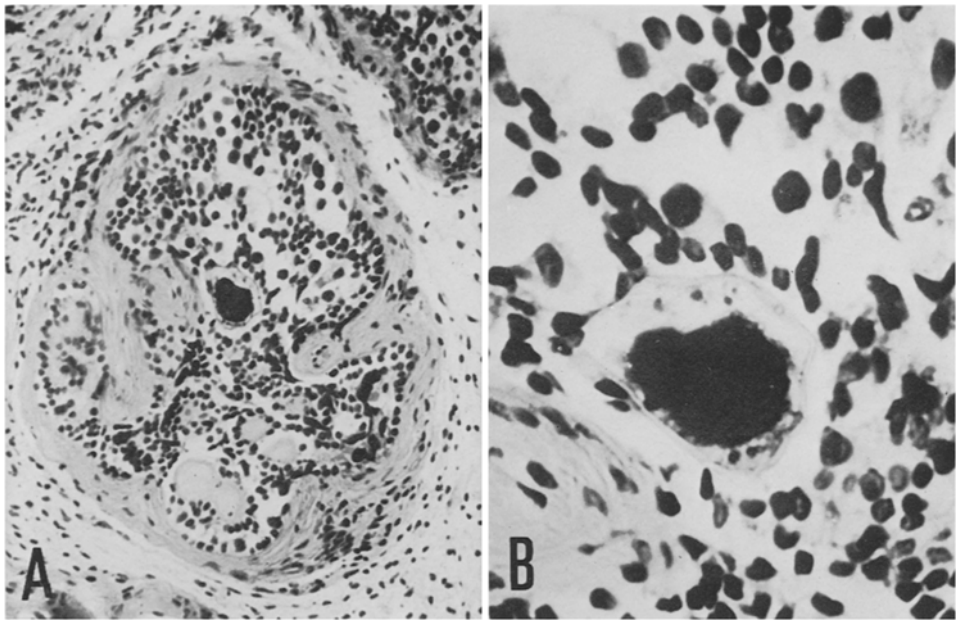

Fig. 1. The histological appearance of gonadoblastoma. A, Rounded nests containing Call-Exner-like body and calcific body; B, Enlarged center field.

Upon physical examination on admission, the patient was 148.0 cm tall and 58.0 kg in weight. All of the following signs were negative: webbed neck, low hair-line, short neck, shield chest, cubitus valgus, hypoplastic nail, pigmented naevi, congenital heart disease, defective hearing, mental defect, and short metacarpal IV. Breast development was normal. Pubic hair was scanty, and axillary hair not present. External genitalia was normal without clitomegary. Internal examination revealed normal vagina, 7 cm in length, and small uterus. Preoperative hormonal and plasma examination revealed an elevation of LH and FSH. LH-RH test indicated a type of hypergonadotropic hypogonadism (Table 1). An abdominal total hysterectomy and bilateral salpingo-oophorectomy were carried out. Residual gonadoblastoma was found in both streak gonads.

CYTOGENETIC FINDINGS

The X chromatin was found in 24% of cells from buccal smear. Analysis of polymorphonuclear leucocytes from peripheral blood smear revealed the presence of drumsticks in 2.7% of cells examined. The Y chromatin was negative in cultured skin fibroblasts and blood cells stimulated with phytohemagglutinin (PHA), as well as in cells from tumor tissue smear. Modal chromosome number of 46 was established on 30 and 50 metaphases from cultured skin fibroblasts and PHA-stimulated blood cells, respectively. Karyotype analysis with Q- and R-banding techniques

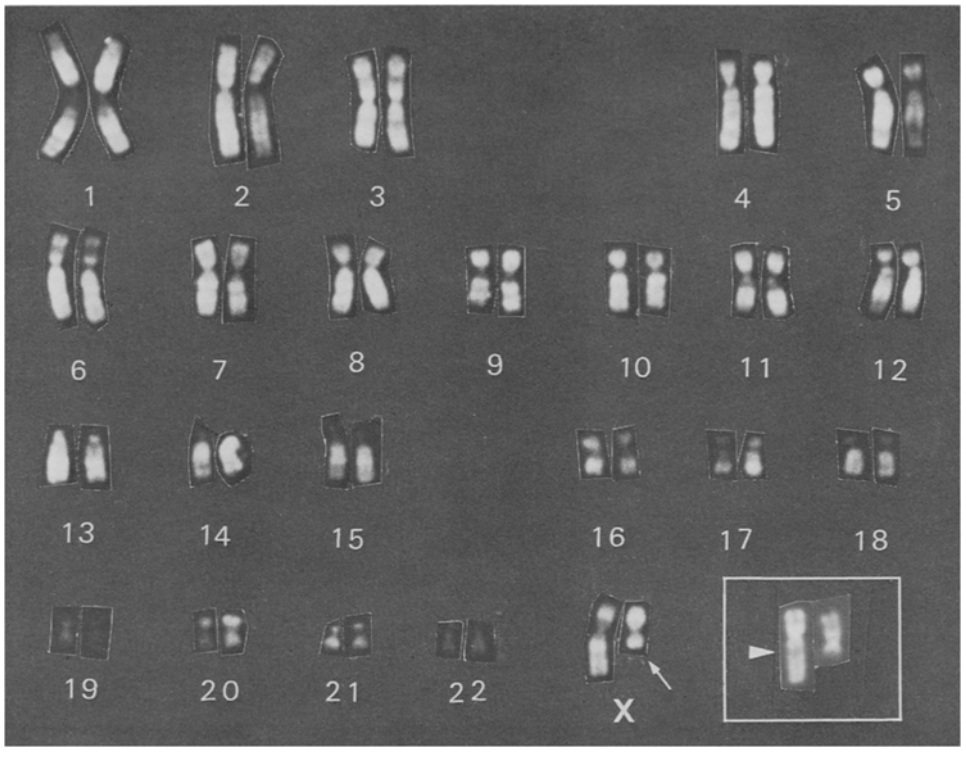

Fig. 2. Q-banded karyotype of a cell with 46,X,del(X)(q21) from a peripheral blood culture with PHA. An arrow indicates the Xq−. R-banded X chromosomes are shown in the inset and the breakpoint, q21, is pointed.

(Niikawa and Kajii, 1975) unequivocally showed that the both types of cells had an aberrant X chromosome with terminal deletion of the long arm at band q21, *i.e.* del(X)(q21), as the sole karyotypic anomaly (Fig. 2). There was no sign of translocation of the deleted material from the Xq− to any other member of the complement. No karyotypic mosaicism was found in blood cells as well as in skin fibroblasts. The BrdU-acridine orange technique (Dutrillaux *et al.*, 1973) provided evidence that all of the Xq− observed exhibited a late-replicating pattern (Fig. 3). No karyotypic abnormality was found in cultured peripheral blood cells from the parents.

DISCUSSION

Although the female phenotype with dysgenetic gonads and the Y chromosome is a regular feature of gonadoblastoma patients (Schellhas, 1974; Hart and Burkons, 1979; Sandberg, 1980), at least five cases of gonadoblastomas without the Y association have been reported to date (de Bacalao and Dominguez, 1969; Salet *et al.*, 1970;

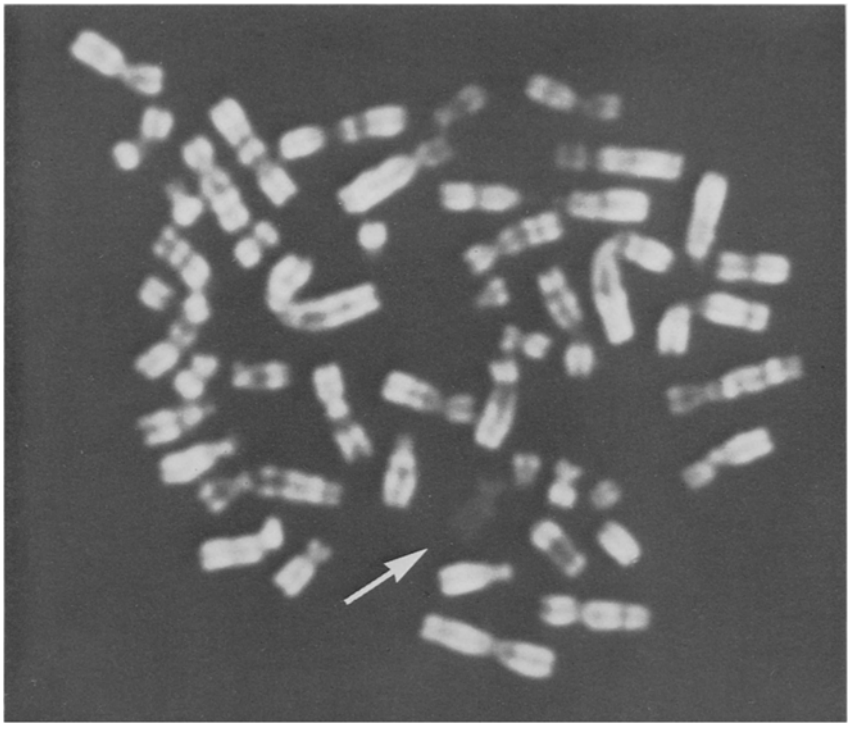

Fig. 3. A skin fibroblast metaphase stained with BrdU-acridine orange technique. An arrow indicates the late-replicating Xq−.

Sandberg, 1980). One exceptional case reported by Williamson *et al.* (1976) was the only phenotypic male with hermaphroditism, in that a fluorescent Y body was detected in cells from the tumor tissue, in spite of the fact that no Y body was observed in the vaginal and buccal smears as well as in the peripheral blood cells of the patient. The present case showed no Y body in both tumor cells and cultured cells from peripheral blood and skin, and the Xq− anomaly was the sole karyotypic abnormality without evidence of mosaicism. The association of the Xq− anomaly with gonadoblastoma seems to be new to our knowledge, although some 17 cases of Xq− patients have been reported to be associated with gonadal dysgenesis.

The breakpoint of the Xq− in the present case, q21, was identical to that in the reported cases of Xq− with or without Turner's stigmata (Boczkowski and Mikkelsen, 1973; Branković *et al.*, 1979). Thus the present case which showed no obvious Turner's stigmata except for mild short stature seemed to be not appreciated for deletion mapping of the Xq−, in agreement with the view of de la Chapelle *et al.* (1975) on karyotype-phenotype correlations, even though a possible association of the Xq− with clinical features of Turner's syndrome and pure gonadal dysgenesis has been stressed by several authors (Bocian *et al.*, 1971; Jenkins and O'Rourke, 1974; Farabosco and Dallapiccola, 1974).

The present findings and those reported previously suggest that the presence of the Y chromosome is not necessarily required to, though may highly favor, the development of gonadoblastoma. Another factor to be considered is unusual endocrine environment in subjects with gonadal dysgenesis, since hormonal levels, such as serum gonadotropin concentrations, usually elevate in this disease (Winter and Faiman, 1972), as do in our present case. If this is the case, the possibility may not be excluded that hormonal medication performed over the years might have exerted certain promoting effect on the tumor development in the present case.

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