47. Klinefelter's Syndrome with 46,XY/47,XXY/48,XXXY Mosaicism

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(Communicated by Sajiyo MAKINO, M. J. A., Sept. 12, 1981)

Among many different types of sex chromosome mosaicism demonstrated so far in Klinefelter's syndrome, 5 cases of triple mosaicism consisting of XY/XXY/XXXY (Jackson *et al.* 1965; MacSween 1965; Ayraud *et al.* 1970; Roman 1974) and 1 of XY/XXY/XXxY mosaicism with a partially deleted x in the XXxY cell line (Hsu *et al.* 1966) have attracted special attention. The patients with such a triple mosaic type have been known to be associated with a variety of clinical features.

In this paper we wish to present clinical and cytogenetical findings of a patient showing some clinical signs of Klinefelter's syndrome, and carrying remarkable triple chromosomal mosaicism with an XY/XXY/XXXY constitution.

Case report. The patient, a 30-year-old male, was first seen in the Dept. of Internal Medicine, Tottori University Hospital in 1979, because of small testes and involuntary infertility during 1 year of marriage. The patient was the second child in 3 male siblings of a family. His nonconsanguineous parents were 30 years of age at the time of his birth. Family history revealed no endocrine abnormality and sterility. His brothers have children in marriage. The pubic hair growth of the patient started at 12 years of age, and he had experienced penile erection and ejaculation. But he noticed his small testes at the age of 20. He appeared to be of normal intelligence. After finishing his high school course he served 4 years in a company, and then he became a staff-member of the town office.

On physical examinations the patient was 168.8 cm tall, weighed 53 kg, and had an arm span of 165 cm. The remarkable findings were as follows: Female escutcheon, sparse body hair, average-sized penis, and atrophic testes measuring 2.1×1.7 cm in the right and 2.3×2 cm in the left. There was no gynecomastia (Fig. 1). He was myopic and his vision was 0.1 uncorrected in both eyes. Physically others were within almost normal limits. On Wechsler Adult Intelligence Scale his full-scale IQ was 90. His electroencephalogram was suggestive

of some abnormalities including spike and wave complexes.

X-ray examinations of the skull, chest, abdomen and extremities revealed no evidence of abnormality. An intravenous pyelogram was also within normal limits. Routine laboratory studies detected normal urinalysis, complete blood count, and biochemical profiles.

Figs. 1, 2. 1: Profile of the patient, at the age of 30 years. 2: Histologic pictures of testis, showing atrophic and hyalinized tubules (A), and spermatogenesis in only one small group of tubules (B).

The results of various endocrine examinations, excluding those of gonadal functions and PRL, revealed normal thyroid functions and adequate TSH production, as well as normal adrenal functions. No anti-thyroglobulin or anti-microsomal thyroid antibodies were detected. The blood sugar and immunoreactive insulin in the oral glucose tolerance test were normal. Repeated basal levels of testosterone were consistently low: 4 values obtained were 1.5, 2.1, 2.4, and 3.3 ng/ml (normal adult males: 4.2 to 12.0). Testosterone failed to increase appreciably in response to hCG (daily im injection of 5000 IU hCG for 3 days) with a maximum level of 3.7 ng/ml. The basal serum gonadotropins were elevated, with LH levels of 58 to 68 mIU/ml (3 to 16) and FSH levels of 80 to 99 mIU/ml (1 to 10). After an iv injection of 100 μ g LH-RH, LH rose to a maximum of 350 mIU/ml (40 to 95) and FSH rose to a peak of 136 mIU/ml (10 to 22). The basal PRL level was 10.2 ng/ml (up to 30), but there was an exag-

gerated PRL response to TRH (500 μ g iv) with a peak of 90 ng/ml (24 to 48).

Azoospermia was recognized by examination of the semen of this patient, the volume of it being 2.2 ml. Histologic examinations of the testicular tissue disclosed various degrees of hyalinization of the seminiferous tubules and large clumps of Leydig cells. Most tubules were small, shrunk and of peritubular fibrous thickening. A few patent tubules were lined exclusively with Sertoli cells, and evidence of spermatogenesis was observed in only 1 small group of seminiferous tubules (Fig. 2).

Cytogenetic studies. The X chromatin investigations were carried out in 500 cells from buccal smears stained with cresylecht violet. Of the cells observed, 13% showed a single X chromatin body and 0.6% had double X chromatin bodies, while the remaining 86.4% were chromatin negative.

Chromosomal studies were undertaken in 2 separate leukocyte cultures established from the patient. Chromosome slides were prepared following conventional Giemsa staining and G-banding methods.

Fig. 3. Partial G-banded karyotypes of the 46,XY cell line (A), 47,XXY cell line (B), 48,XXXYY cell line (C), and 49,XXXXYY cell line (D).

Chromosome analyses demonstrated the occurrence of 3 different stem lines consisting of 46, 47 and 48 chromosomes, respectively. In a total of 110 well-spread metaphase cells, 28 cells with 46 chromosomes, 67 cells with 47 chromosomes and 11 cells with 48 chromosomes were carefully studied. Detailed karyotypic analyses were made in 10 cells in each of the cell-lines. Karyotypic analysis of the 47 cell-line detected the occurrence of 1 Y chromosome and 16 chromosomes in the group C. The extra chromosome was identified as an

X based on its G-banding pattern. Thus the karyotype was determined as 47,XXY in this line (Fig. 3). The examination of the G-banded chromosomes in the 48 cell-line manifested 1 Y chromosome together with 17 chromosomes in the group C, and the extra chromosomes were identified as X's (48,XXXY). The 46-chromosomal cells had a normal male chromosome complement as 46,XY. Analysis of 3 cells with 45 chromosomes indicated that the missing chromosome varied in each cell; most probably they were artefact products. One cell showed a modal count of 49 chromosomes; an XXXXY sex chromosome complement was detected in this cell (Fig. 3). It is then concluded that this cell serves as the 4th stem-line.

Discussion. The present patient was infertile and distinguished by some characteristic signs of Klinefelter's syndrome, such as small testes with hyalinized seminiferous tubules, azoospermia and elevated gonadotropins, although he was normal in stature, of normal intelligence and had some spermatogenic activity. The cytogenetic investigations have made it clear that the present patient can be regarded as of triple mosaicism with the sex chromosome complement consisting of XY/XXY/XXXY. Further, since the 49,XXXXY cell can be taken as a true cell line, the patient is possibly a mosaic case with 4 cell lines, 46,XY/47,XXY/48,XXXY/49,XXXXY. It is noted that 63% of the cells from blood cultures of this patient had an XXY sex chromosome complement.

For the possible mechanism causing this kind of sex chromosome mosaicism, multiple nondisjunctional mechanism has previously been presented (Hsu *et al.* 1966; Kardon *et al.* 1971). The origin of the sex chromosome mosaicism in this patient may most likely be derived from a primary meiotic nondisjunction of the X chromosome resulting in the formation of an XXY zygote, followed by mitotic nondisjunction after the 1st cleavage division during the early post-zygotic stage.

Concerning the karyotype-phenotype correlations, information is available in Klinefelter's syndrome that the physical and mental disability increases along with the number of extra X chromosomes. About half of the patients with 47,XXY have been mentally retarded, and almost all 48,XXXY and 49,XXXXY individuals have been associated with more severe intellectual impairment (Ferguson-Smith 1966).

The literature exemplifies 5 patients of triple mosaicism with an XY/XXY/XXXY complement and one patient with an XY/XXY/XXXp-Y complex. The clinical and cytogenetic findings of these 6 cases are summarized in Table I. Micro-orchidism is apparent in all the 6, while one patient showing about 31% of 46,XY cell line had 2

children (Roman 1974), and another was reported to claim a daughter (Jackson *et al.* 1965). Some spermatogonia with meiotic figures were noted in one case (MacSween 1965). Their heights ranged from 162 to 193 cm, and one was a delinquent (Roman 1974). Three patients carrying a predominant XXY cell line were reported to be of normal intelligence. Intelligence tests in the others with the equivalent proportions of each cell line (Ayraud *et al.* 1970) and with considerably larger proportion of XXXY cells (Hsu *et al.* 1966) showed scores of 86 and below.

Table I. Comparison of the major clinical and cytological findings in the reported cases of mosaicism with 46,XY/47,XXY/48,XXXY and 46,XY/47,XXY/48,XXXp-Y

Authors	Age	Height (cm)	IQ*	Testes (cm) penis	Physical signs associated abnormalities	Barr body (%)		Cells counted				
						1	2	45	46	47	48	49
46,XY/47,XXY/48,XXXY												
Jackson <i>et al.</i> (1965)	55	178	N	small (2.0) small	gynecomastia breast cancer inguinal hernia	42	1	2	7	40	3	
MacSween (1965)	53		N	small (1.5) small	eunuchoid, infertile gynecomastia rheumatoid arthritis reticulum-cell sarcoma varicose ulcer	(89	11)**	5	43	85	4	0
Ayraud <i>et al.</i> (1970)	57	172	R 86	small (0.5) normal	infertile, asthenia oligophrenia somnolence, alcoholism	18	5		(1 : 1 : 1)			
Ayraud <i>et al.</i> (1970)	45	180	R 75	small (0.5) normal	asthenia, oligophrenia somnolence hallux valgus	23	5		(1 : 1 : 1)			
Roman (1974)	63	162	N	small small	eunuchoid, fertile gynecomastia, twin delinquent, evader	30 35	0 0	7	27	55	5	
Present authors	30	169	N 90	small (2.3) normal	infertile myopia	13	1	3	28	67	11	1
46,XY/47,XXY/48,XXXp-Y												
Hsu <i>et al.</i> (1966)	21	193	R	small (2.5) normal	eunuchoid Ehlers-Danlos syndrome syndactyly	34	6	3	47 15	73 20	129 45***	

* N, normal; R, retarded. ** % in positive cells. *** Skin fibroblasts.

The mosaic patients with 47,XXY/48,XXXY (Finley *et al.* 1964; Pashayan *et al.* 1973), 47,XXY/48,XXXq-Y (Crawford 1961), and 47,XXY/48,XXXY/49,XXXXY karyotypes (Guli *et al.* 1967; Tumba 1975) were mentally defective with small testes and a variety of congenital malformations. In contrast Kardon *et al.* (1971) reported a case of 47,XXY/48,XXXY/49,XXXXY mosaicism in a mentally normal boy suspected of having Klinefelter's syndrome because

of a small penis and small firm testes. The peripheral leukocyte and skin fibroblast cultures as well as in testicular fibroblast culture from this patient showed the predominant cell line having 48,XXXY and the second cell line of 47,XXY together with a few 49,XXXXY cells. But 2 XY cells were detected: One in skin fibroblasts and the other in testicular tissue. Therefore, this may be the 1st case as a 46,XY/47,XXY/48,XXXY/49,XXXXY mosaic. It was suggested that his apparently normal intelligence might be attributable to the presence of an XY cell line.

Mosaic individuals sometimes seem to be much less severely affected than patients with pure aneuploidy. Two-thirds of patients with an XY/XXY have been known to be mentally normal, one-third of them being fertile (Ferguson-Smith 1966), and an XY/XXXY mosaic case has been reported to have full spermatogenesis (Barr *et al.* 1962). It is apparent that the presence of a normal XY cell line seems to exert an alleviating effect on the degree of disability. On the basis of the fact that the 47,XXY/48,XXXY individuals so far described have been mentally defective, the absence of mental retardation and the presence of some spermatogenic activity in the present patient seem to support the above concept.

Acknowledgement. The authors are much indebted to Professor Emeritus, Dr. Sajiro Makino, M. J. A., for improvement of the manuscript with valuable advices.

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