Isochromosome for Long Arm of Y Chromosome in Patient with Turner’s Syndrome and Sex Chromosome Mosaicism (45,X/46,XYq1)

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In patients with structural aberrations of the sex chromosomes a direct relation has been found between the phenotype and the extent and site of sex chromosomal deletion (Ferguson-Smith, 1965, 1969). Women with deletion of the short arm of the X chromosome invariably have short stature and streak gonads, and usually have several of the other malformations of Turner’s syndrome, while those whose X chromosome deletion is confined to the long arm have shown only the gonadal defect. Deletions of the Y chromosome have also been found in Turner’s syndrome, usually in association with 45,X mosaicism. In several cases, including some with presumptive short arm isochromosome of the Y, there have been ambiguous external genitalia and signs of incomplete testicular differentiation. The possible genetic implications of these findings are that the Y chromosome may bear X homologous loci, and that the short arm of the Y chromosome may bear the determinants of male sex differentiation. This hypothesis is strengthened by the findings in two patients with isochromosomes for the long arm of the Y chromosome (Jacobs and Ross, 1966) who show female sex differentiation. A third example of this apparently rare type of Y chromosome aberration is described here in a patient found at necropsy to have minor degrees of masculinization of the internal and external genitalia.

Case Report

An unmarried woman aged 66 years was born on May 11, 1900, when her mother and father were aged 22 years and 35 years, respectively. She had two younger sibs, a brother 64 years old and a sister 50 years old. In June 1966 she was admitted from a farm in Fife where she had been employed in terms of arrangements made by the Local Authority for Boarded Out Mental Defectives. She seemed alert, but was uncooperative and gave a poor history. Her presenting complaints were pain at the base of the chest, breathlessness, and swelling of the hands and feet. Her past history was uninformative with the exception of scarlet fever which required hospital admission at the age of 8 years. She had never menstruated.

Physical Examination. The patient was an obese woman of short stature (147 cm.) with a dull expression and poor intellect. The skin was pale and there was peripheral cyanosis and oedema of the face and extremities. A varicose ulcer was present on the lower part of the right leg. She had dysphonia, the breath was offensive, and there was jugular venous congestion and triple rhythm. Her blood pressure was 170/110 mm. Hg and the fundi showed moderate hypertensive retinopathy. The respiration rate was increased and there were crepitations and rhonchi over both lung fields with signs of consolidation at the left base. The abdomen was obese, showed striae, and there was eversion of the umbilicus.

The external genitalia showed clitoral enlargement and rudimentary labia minora, but no fusion of the labia. Pubic and axillary hair were scant and there was no breast development. She had a short neck and shield-shaped chest with widely-spaced nipples and small areolae. The IVth metacarpals and metatarsals were short and the finger-nails and toe-nails were hypoplastic. She had bilateral cubitus valgus, and multiple small pigmented naevi were noted over the trunk and limbs. Chest x-ray showed cardiomegaly and pulmonary congestion, with extensive consolidation of the left lower lobe. The electrocardiogram was consistent with myocardial ischaemia. Blood urea was 58 mg./100 ml. The haemoglobin was 10.2 g./100 ml., with PCV of 35% and MCHC of 29%; the blood film showed a hypochromic normocytic anaemia. There was a leukopenia of 3900/cu.mm. Urinary culture was sterile, but red
cells were noted. Electrolytes, faecal occult blood test, and liver function tests were normal. During investigation of the haematuria, attempts at catheterization failed because of an unusual configuration of the urethra.

The patient responded at first to treatment of the chest infection with oxytetracycline and ampicillin, and to treatment of the congestive cardiac failure with digoxin, mersalyl, and frusemide. Haematuria persisted, however, and the patient developed a urinary infection with *Esch. coli* which was unresponsive to treatment. She became severely uraemic with oliguria, developed bilateral bronchopneumonia, and died 33 days after admission.

**Necropsy.** The lungs showed extensive confluent bronchopneumonia involving all lobes, especially the left lower lobe where there was early abscess formation. Apart from minimal atheroma, no abnormality was noted in the cardiovascular system. The kidneys were of normal size and showed only congestion. The urinary tract was normal. The remaining abdominal viscera showed terminal congestion only. The thyroid (30 g.) was slightly enlarged; the left lobe was nodular, and contained a small calcified adenoma. Over the left cerebral hemisphere, including the temporal lobe, was an old subarachnoid haemorrhage, 0·8 cm. thick. The underlying brain (960 g.) showed flattening and a shallow depression in this area. No intracerebral abnormality was noted and no source of the old subarachnoid haemorrhage could be detected.

The uterus was infantile, measuring 6 cm. from the fundus to the exocervix. It was 4 cm. in breadth and the antero-posterior diameter was 1·5 cm. The fallopian tubes were each 9 cm. in length and 4 mm. in maximum diameter. At the fimbrial end of each tube there were several small fimbrial cysts, measuring up to 1 cm. in diameter on the right side and 3 mm. on the left side. In the left broad ligament a thin ridge of tissue was found; and in the position of the right ovary there were a few small cysts, maximum diameter being 8 mm. All were removed for histological examination. The uterus had an endometrial lining containing inactive glands, and simple coiled tubules lined by mucus-secreting cells were numerous in the wall of the endocervix. Sections taken at the fimbrial ends of each fallopian tube showed mucin-containing fimbrial cysts lined by flattened epithelium and, on each side, an additional tubular structure with a thick smooth muscle coat which was interpreted as part of a rudimentary mesonephric duct. The left gonad (Fig. 1) consisted of fibrous ovarian-like stroma in which were tiny cystic spaces, lined by cuboidal epithelium, and a few mesonephric tubules. No primordial follicles were seen, and the appearances corresponded to those of a streak gonad. No gonad was found on the right. The cysts in the ovarian position in the right broad ligament were lined by flattened epithelium. No seminiferous tissue was identified, but in the fibrous stroma surrounding these cysts were numerous closely-packed tubules, with muscular walls and lined by ciliated columnar epithelium, the appearances being similar to those of epididymis (Fig. 2).

**Cyto genetic Findings.** Chromosome preparations were made from 72-hour lymphocyte cultures in the patient and her brother. All cells were fully analysed by direct microscopy and, in some cells, photographic analyses were also made. As indicated in the Table, about 85% of the patient's lymphocytes had a 45,X chromosome constitution. The cells with a count of 46 had, in addition, a small exactly metacentric chromosome, slightly larger than chromosomes 19-20 (Fig. 3). In several of these cells, the distal ends of this abnormal chromosome showed the negative heteropyknosis characteristic of the distal end of the long arm of the normal Y chromosome. In some cells the chromatids of this chromosome were more closely approximated to one another than any of the other small chromosomes in the cell, which is again typical of the Y chromosome.

Buccal smears and necropsy material from several tissues were examined for sex chromatin and found to be chromatin negative. Chromosome analysis in the brother revealed an apparently normal male karyotype (Table), and a buccal smear was chromatin negative. The Y chromosome was
of normal appearance and was consistently much smaller than chromosomes 19–20.

A comparison of the patient's karyotype with her brother's karyotype showed that the abnormal metacentric chromosome was much larger than the brother's Y chromosome. The findings were consistent with the interpretation that the abnormal metacentric was an isochromosome for the long arm of the Y and not, for example, a pericentric inversion of the Y, a dicentric Y chromosome, or an X chromosome aberration.

Colour vision was normal and the Xg blood group was Xg(a−) in both brother and sister.

Comment

The patient had the classical features of Turner's syndrome comprising short stature, sexual infantilism, and characteristic multiple developmental malformations. Such a phenotype is to be expected in a chromatin-negative individual with a 45,X cell line. The masculinization and abnormal development of mesonephric structures is an unusual accompaniment of a 45,X karyotype, and it seems reasonable to attribute these changes to the 46,XYqi cell line rather than to postulate an undetected third cell line with a normal Y chromosome. (There are few exceptions to the general rule that any degree of male differentiation in Turner's syndrome is associated with a Y chromosome, or part of a Y chromosome, in at least a proportion of cells (see Ferguson-Smith, 1965). The few exceptions can probably be adequately explained on the basis of undetected mosaicism for a cell-line carrying a Y chromosome.) The findings in our case thus differ from those in the two non-mosaic patients of Jacobs and Ross (1966). These two cases showed no obvious evidence of male differentiation, and this gives strong support for the localization of male determinants to the short arm of the Y chromosome. It is therefore important to establish that the chromosome aberration in our case is a long-arm isochromosome of the Y and not, for example, a pericentric inversion of the Y or a dicentric Y chromosome (which both contain short arm...

### TABLE

RESULTS OF CHROMOSOME ANALYSIS

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<td>Sex chromosome constitution</td>
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Fig. 2. Section of tissue from the right ovarian site showing closely-packed tubules lined by ciliated columnar epithelium. (Haematoxylin and eosin. ×125.)
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FIG. 3. Karyotype analysis showing the presumptive isochromosome for the long arm of the Y chromosome present in about 15% of the patient's lymphocytes. (Aceto-orcein. Reduced from ×4000.)

material). Fortunately, the cytological features of the abnormal chromosome are quite characteristic. It seems exactly metacentric, the centromere is clearly single, and both arms are identical in appearance, with closely approximated chromatids and both ends showing the negative heteropyknosis characteristic of the distal end of the long arm of the Y. In patients with pericentric inversions of the Y it is usual to find that close male relatives have the same variation (Jacobs, 1969). The observation of a normal Y chromosome in the patient's brother can be taken as further evidence against the diagnosis of a pericentric inversion.

One must conclude, therefore, that the most likely interpretation of the chromosome analysis in our patient is 45,X/46,XYqi mosaicism. The presence at necropsy of a rudimentary epididymis and other mesonephric structures suggests that during embryogenesis there was a right gonad which had sufficient testicular differentiation to induce some development of the Wolffian ducts, but which later regressed under the influence of the ovarian tissue on the left. If this explanation is correct, it may imply that factors on the long arm as well as on the short arm of the human Y chromosome play a part in male determination.

Summary

A patient with Turner's syndrome and sex chromosome mosaicism of the 45,X/46,XYqi type was found at necropsy to have minor degrees of masculinization of the internal and external genitalia.

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REFERENCES


