42. An Atypical Turner's Syndrome Case with a Long Arm Iso-X Chromosome*)

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Recent information indicates that chromosome abnormalities, particularly of sex-chromosomes, occur rather frequently in patients with clinical signs of primary and sometimes secondary amenorrhea. In general clinical defects such as rudimentary gonads, short stature, webbed neck, cubitus valgus and some other external anomalies are noted as characteristic Turner's stigmata, thus forming a recognizable disease picture. Following Fraccaro et al. (1960) who described first a presumptive iso-X chromosome in three chromatin positive primary amenorrhea patients with Turner's symptoms, the presumptive isochromosome for the long arm of the X chromosome has been reported in many Turner's cases as a rather common chromosomal variant. Generally Barr bodies and drumsticks are more frequent and larger in those cases than in normal XX females (Jacobs et al. 1961).

While working on a broad chromosome survey in sex-anomalous patients, we have chanced to observe an iso-X chromosome in a patient with secondary amenorrhea and somewhat atypical stigmata of Turner's syndrome.

Materials and methods. Leucocyte cultures were carried out according to the standard method. Autoradiographic techniques based on blood cultures followed those described by Giannelli (1963) with minor modifications. The skin cultures were prepared according to the plasma-clot method. Barr bodies were analyzed on buccal smears stained with acetic orcein.

Clinical notes. A 20-year-old, phenotypical female (Fig. 1) was hospitalized due to secondary amenorrhea and sexual infantilism. She was born after an uneventful pregnancy with a birth weight of 3,000 g. The mother was 30 years old and the father 35 years. Both parents are of normal height, being 153 cm for the mother and 172 cm

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for the father. The proposita is the fifth daughter of a sibship consisting of two males and four females, and is apparently the only one presenting abnormal findings. She is of average intelligence and was graduated from a high school with a middle grade. She has the following characteristics: weight 40 kg; height 147 cm (−1.2 S.D.);

span 150 cm; upper segment 76.5 cm; lower segment 67.5 cm; head circumference 58 cm; chest width 72 cm; chest circumference 77 cm; and nipple distance 18.5 cm. The ears were slightly low-set and prominent; there was ptosis of the eyelids bilaterally; the hard palate was narrow and acutely arched; the neck was short but without webbing; the shoulder-girdle was masculine and the chest was broad and shield-like, showing little breast development and pigmented nevi over the skin of the neck. The external genitals were infantile, without secondary hair growth in both axilla and external genitals. She had menarche when 19 years old, without having afterward spontaneous uterine bleeding. A slight uterine hemorrhage was noted after therapy with progesterone, 250 mg. No evidence was shown for dichotomy in her basal body temperature. Urinary 17-KS were estimated as 3.0 mg/day, and 17-OHCS, 12.5 mg/day. No evidence for color-blindness was obtained.
Dermatoglyphic patterns. The palmar dermal pattern (Fig. 2) was characterized by high axial triradii (26 per cent at right and 42 per cent at left), and the bilateral third interdigital loops with a normal a-b ridge count (36 at right, 39 at left). The simian line was absent in both palms. The hypothenar areas were patternless.

Cytological findings and remarks. Oral smears showed chromatin positive cells at 27 per cent. In most cells studied, Barr bodies seemed to be apparently larger than normal (Fig. 3). Results of chromosome counts in blood and skin cultures from the patient are summarized in Table I. The patient gave a modal chromosome number of 46 in both samples. Cells with the modal chromosomes were karyotyped and showed consistently 44 well-defined autosomes classified into group A to G, one typical X chromosome and one outstanding large element. The latter unusual chromosome had two arms of a similar length corresponding in size to the chromosomes no. 3.

Recently autoradiographic techniques with tritiated thymidine have been employed as useful tools for the identification of chromosomes on the basis of their replicating pattern in normal and abnormal human cells. Autoradiographic studies provided the evidence that in 35 of 38 metaphases examined, the outstanding chromosome similar in size to no. 3 showed a prominent late replication of its DNA, and further, in 26 metaphases the labeling pattern was symmetrical between the two similar arms forming that chromosome, leaving an unlabeled gap in the centromere region (Figs. 4-5). It has been shown that the iso-X chromosome of the long arm undergoes generally DNA replication later than the autosomes (Giannelli et al. 1963), and that it begins replication almost simultaneously with no. 3 autosomes (Mukherjee et al. 1966). The iso-X chromosome is thus distinguished by a characteristic symmetrical labeling pattern in the two arms (Ockey et al. 1965). In the light of the above consideration, it is very likely that the outstanding element similar to no. 3 chromosomes is a long arm iso-X chromosome. The occurrence of the large-sized Barr body in this patient is supplementary for this interpretation.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Chromosome counts</th>
<th>No. of cells obs.</th>
<th>No. of cells anal.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Blood</td>
<td>1</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>2</td>
<td>49</td>
<td>2*</td>
</tr>
</tbody>
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* Due to two unusual metacentric chromosomes corresponding to no. 3.
Isochromosomes are generally considered to be formed as a result of misdivision of the centromere (de la Chapelle et al. 1965). The patient with an isochromosome for the long arm of an X chromosome is hence effectively monosomic for the short arm. It has been reported that the long arm iso-X chromosome is generally associated with Turner's syndrome or related disorders with short stature.

Fig. 4. Karyotype of a leucocyte metaphase and the autoradiogram placed underneath. The presumptive iso-X chromosome (arrow) is late and heavily labeled.

Fig. 5. Partial karyotypes and autoradiograms from two leucocyte metaphases, showing comparatively heavy and symmetrical labeling pattern in the iso-X indicated by arrows.

Jacobs et al. (1961) suggested the possibility that genes controlling growth may be located on the short arm of the X chromosome. Information is available that short stature is associated with a deletion of the short arm of an X chromosome, and that the loss of the long arm of an X chromosome is not necessarily associated with short stature (Jacobs et al. 1961; Ferguson-Smith et al. 1964). In our
case, the finding of a rather normal stature seems to be quite unusual in respect of the monosomy for the short arm of the X.

Summary. A long arm iso-X chromosome was described in a chromatin positive patient, with clinical signs of atypical Turner's syndrome together with secondary amenorrhea, on the bases of autoradiography and buccal smear studies. A correlation between the iso-X and Turner stigmata, particularly short stature, was considered.

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References