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**Turner's Syndrome Variant with Three Cell Line Mosaicism
and Ring X Chromosome (45, X /46,X r(X)(p21 q25)/46, Xx)
in A Saudi Patient**

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A case of Turner's Syndrome with three cell line mosaicism associated with ring X Chromosome, which is an extremely rare condition. Perhaps this is the first case report, with such chromosomal abnormality, from Saudi Arabia. The phenotypical changes are comparable with classical Turner's Syndrome of 45, X complement. The other findings are also discussed.

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Turner's syndrome is the most common sex chromosomal abnormality in females, affecting an estimated 3 percent of all females conceived. However, the frequency among live born female infants is only 1 in 1500 to 1 in 2500, and as many as 15% of spontaneous miscarriages have a 45,X karyotype. It is estimated that only 1 in 100 embryos with 45, X karyotype survive to term¹. More than half of all patients with Turner's Syndrome have mosaic complement^{2,3}. The frequency of physical abnormalities in Turner's Syndrome vary with the pattern of karyotype⁴. The article presents a case with three cell line mosaicism combined with ring X chromosome, which is quite rare.

THE CASE

A 20 year old Saudi female from a medical ward of Dammam Central Hospital presented with bronchiectasis, diarrhoea and failure to thrive since birth and was suspected as a case of Cystic Fibrosis.

The patient had sickle cell trait and α thalassaemia. She had not attained menarche.

She was short statured with 118cm in height and 20kg in weight, marked dorsal kyphoscoliosis with convexity to the left. She was partially deaf and mentally subnormal. She had clubbing, conjunctivitis and small breasts. On auscultation, the lungs showed creptations. The cardiovascular and gastro-intestinal tract were normal.

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Figure. Karyotype of the patient showing the Ring X Chromosome.

Routine biochemical investigations were within normal limits except for raised amylase and alkaline phosphatase and decreased glucose levels. Rest of the findings were within normal limits.

Microbiological investigations showed sputum negative for AFB. Stool examination revealed Giardia Lamblia and Trichomonas Hominis infestation.

Radiologically, the chest showed kyphosis of lower cervical and upper thoracic vertebrae, with distorted thoracic cage due to crowding of the ribs. Bilateral bronchiectatic changes were seen with calcified hilar areas suggestive of healed tuberculosis.

Ultrasonography findings of pelvic organs showed a small uterus, normal left ovary and the right ovary was not visualized.

The chromosomal analysis done by Peripheral blood lymphocyte culture and G – banded, showed a novel mixoploidy of 45,X /46,Xr (X)(p21 q25)/46,XX complement in the ratio of 75:20:5 respectively. Sex chromatin was negative.

A diagnosis of Turner Syndrome variant with ring X chromosome was made.

DISCUSSION

Very few articles are available in the literature with three cell line Turner's mosaicism combined with ring X chromosome. Of the available articles on ring X chromosome and mosaicism, authors differed in their opinions regarding phenotypic changes.

A ring chromosome is formed when breaks occur at both ends of a chromosome and proximal ends rejoin. The acentric fragments are usually lost and partial monosomy results. In practice ring chromosomes induce complex mitotic events with variable duplication, deficiency and unpredictable phenotypic expression. It is mentioned that Ring X chromosome cases differ phenotypically according to the size of the ring, reflecting the amount of deletion of both short and long arms. The smaller the ring, the greater the deletion and closer the resemblance to classic XO Turner phenotype⁵. Some author's felt that the ring X chromosome patients lacked many of the Classic

Turner's syndrome features and majority are not karyotyped until after the age of 11, usually because of the pubertal failure⁵ and also others believed the phenotype is more severely affected than expected in Classical Turner's syndrome⁶⁻⁹. The consistent features associated with ring X chromosome are growth failure, mental retardation, atypical facial appearance and skeletal anomalies. All these features are also seen in Classical Turner's Syndrome but in varying degrees but rarely affected by mental retardation, as was observed in 21 cases from 1965–1989¹⁰. The patients with ring X chromosome are reported with typical features of Turner's Syndrome¹¹.

Some reported severe mental retardation in 2 cases with neurological abnormalities, coarse face and syndactyly involving upper and lower limbs. Each had mosaic variant with ring X chromosome¹⁴. The present cases was mentally retarded.

Webbing of the neck, which is a common feature of 45,X Turner's Syndrome is less frequent in cases with ring X ring chromosome patients are of shorter stature than expected in Turner's syndrome⁷. The growth retardation may be the direct genetic effect of chromosomal deficiency¹¹.

In the skeleton, vertebral column deformities are more common in Turner's Syndrome in general and specifically with ring X chromosome. Vertebral column deformity may lead to further reduction of the height of the patient¹. Some authors reported the abnormality of bone structure in Turner's syndrome and more so in ring X chromosome condition in the form of osteoporosis seen radiologically. It is not known whether this feature is a congenital abnormality of skeletal structure or an acquired feature related to hormonal deficiency¹¹. Others found on radiological examination an overall diminished bone density. There was flattening of the vertebral bodies, particularly in thoracic region, vertebral body ossification is incomplete and posterior elements of the spine showed no ossification¹². Some felt severe osteoporosis leads to vertebral collapse and may produce vertebral column deformities¹⁶. One author described that hypoplasia of the first cervical vertebra and unequal development of dorsolumbar plates was responsible for vertebral column malformations¹⁹. This particular case, although had ring X chromosome in association with the mosaic pattern, showed more or less the same phenotypical changes that are seen in the classical Turner's syndrome. The further reduced height of the patient may be due to kyphoscoliosis due to osteoporosis and demineralization of bones specifically in the vertebrae. However, it can not be ruled out that tuberculosis precipitated kyphoscoliosis in this case as the radiological examination of the chest revealed findings of healed tuberculosis.

As in all X chromosomal abnormalities, primary amenorrhoea was expected in this case too. The diarrhoea cannot be explained unless it was due to the parasitic infestation, although there is an increased incidence of Crohn's disease and ulcerative colitis in Turner's Syndrome¹. Increased amylase might be due to the intestinal stress and the raised Alkaline phosphatase is usually seen after menopause and bone disorders, as expected in Turner's syndrome.

Small breast development is attributed, perhaps to the 46, XX cell line that is present in the karyotype and normal left ovary in ultrasonography findings. 20% to 25% girls with Classical Turner's Syndrome have breast budding due to residual ovarian function¹.

The partial deafness might be due to congenital anatomical distortion of the eustachian tube¹, again a feature of Turner's syndrome. A ring chromosome derived from one of the X chromosomes has been observed occasionally in women with infertility¹⁸, in female hemophilia with 46,XXr/45X karyotype and signs of Turner's Syndrome¹⁹, and a rare association of chromosomal, immunological and endocrine defects is described in young woman with short stature, recurrent pulmonary infections and primary amenorrhoea with karyotype of 45, X/46x r(X) (p22 q27) of peripheral blood lymphocytes. Severe immunodeficiency was revealed by phenotypical and functional studies and a selective gonadotrophin defect was disclosed by endocrinological investigations²⁰. It is very surprising why this young girl was not investigated till recently for Turner's syndrome in spite of the fact, that she had all the classical features! Fortunately, the patient had no other systemic abnormalities. Only two articles with three cell line and four cell line mosaicism associated with ring X chromosome and other structural aberrations are available. In both these cases the phenotypic features are almost similar to that of classical Turner's syndrome^{20,8} and are consistent with the authors' findings in the present case, which might be the first case report from Saudi Arabia.

CONCLUSION

This case with such rare chromosomal defects was not reported from Saudi Arabia nor from rest of Arab world as far as we could see. We are concerned about the delay in her diagnosis, which emphasize the importance of screening the newborns for signs of Turner syndrome, which suspected then the baby should have full chromosomal study.

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