Case report

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A rare disorder of sex development: de la Chapelle syndrome

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ABSTRACT

Sex reversal syndromes can be summarized as incompatibility of chromosomal sex and gonadal characteristics. A very rare syndrome. 46 XX testicular disorder was first described by De La Chapelle in 1964 in 46 XX karyotype, male individuals. Generally, patients whose phenotype is male apply to the health center with infertility, impotence, loss of libido or gynecomastia. The translocation of the part of the Y chromosome, including the SRY (sex-determining region Y) gene, to the X chromosome during paternal meiosis is responsible for etiopathogenesis.

In our case, a 38-year-old male patient applied to our outpatient clinic with the complaint of enlargement in both breasts. His beard-mustache and body hair distribution were normal, he has bilateral grade 2 gynecomastia, penis length was 7 cm, testicles were small, and palpable in the scrotum. Laboratory values were compatible with hypergonadotropic hypogonadism and in the sperm analysis azoospermia was detected. Karyotype analysis was 46 XX, SRY was also studied with FISH (Fluorescence in Situ Hybridization) technique. The patient was diagnosed with 46 XX Testicular Disorder (de la Chapelle Syndrome) and testosterone replacement therapy was started.

We aimed to present the diagnosis and management of De La Chapelle Syndrome in our case.

Keywords: Disorder of sex development, gynecomastia, 46 xx males

Sex reversal syndrome can be summarized as the incompatibility of chromosomal sex and gonadal characteristics. 46 XX testicular disorder is a very rare syndrome that was first described by De La Chapelle in 1964 in men with a 46 XX karyotype. [1] It is seen in one in 20000 newborns. [2] In the classic type, individuals are usually male phenotype and of normal height. Somatic anomalies are not expected, and intelligence is normal. [3] Although the testicles are located in the scrotum, they are quite small in size. Gynecomastia is common. No fertile cases have been reported, azoospermia and infertility appear in every case. Although very rarely, spermatogonia can be found in the ejaculate. [4] In addition to the classical type, there are also variants with ambiguous genitalia and true hermaphroditism. [5] Generally, the reasons for admission to the hospital are gynecomastia and infertility.

CASE REPORT

A 38-year-old male patient was admitted to the Sultan Abdulhamid Han EAH Endocrinology and Metab-

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olism Diseases Outpatient Clinic with the complaint of enlarged breasts. He stated that the enlargement of the breast had been for many years. He did not have any comorbidities or any medication that he used regularly. He complained of sexual reluctance, erectile dysfunction and absence of ejaculation. Although he has been married for 12 years, he has no children. On physical examination his height was160.9 cm, weight was 75.2 and body mass index was 29. There were grade 2 gynecomastia in both breasts, more prominent on the right. Penis length was 7 cm. Although the testicles were smaller than normal, they could be palpated in the bilateral scrotum. In laboratory tests, TSH: 0.7006 uIU/mL (0.35-4.94), Free T4: 1.05 45 ng/dL (0.7-1.48), Total Testosterone: 1.04 ng/mL (1 .66-8.11), Prolactin: 7.66 ng/mL (3.46- 46 19.40), FSH: 34.13 mIU/mL (0.95-11.95), LH: 12.51 mIU / mL (0.57-12.07), Estradiol (E2): < 10 pg/mL (11.3-43.2).

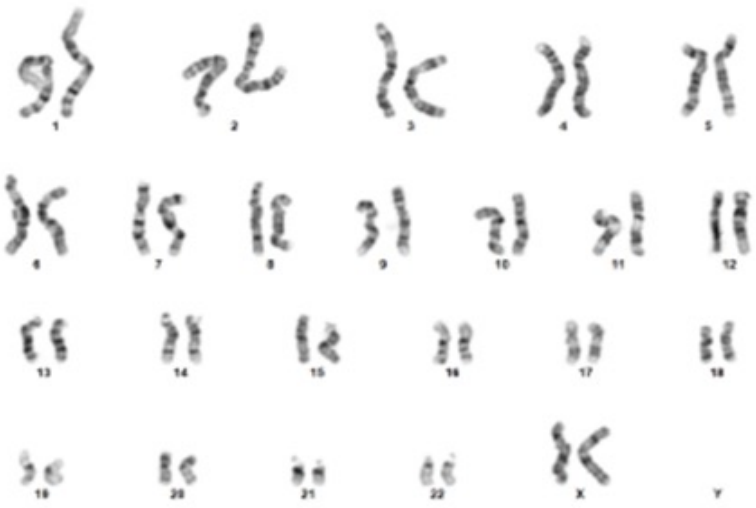
Breast ultrasonography was performed: There is bilateral gynecomastia, more prominent on the right. No mass lesion was observed. His mammography: Bilateral gynecomastia appearance is present. Breast density was more prominent in the right breast. His scrotal ultrasonography: Right testis was 15 x 9 x 15 mm (1.1 cc), left testis was 17 x 10x13 mm (1.3cc), and testis dimensions were reduced.

Karyotype analysis was requested from the patient. The karyotype analysis revealed 46, XX (Fig. 1). Simultaneous microdeletion analysis revealed deletion in AZFa AZFb AZFc regions. SRY was positive in amplification by FISH (fig. 2).

After all these examinations, the patient was started on 100 mg of testosterone decanoate and gradually the dose of 300 mg/month was reached. No side effects were observed that would cause the patient to discontinue treatment. He stated that there was an improvement in sexual functions. The patient was screened for osteoporosis by bone mineral densitometry. No osteoporosis or osteopenia was detected. After explaining the current illness to the patient, he was referred for psychosocial support.

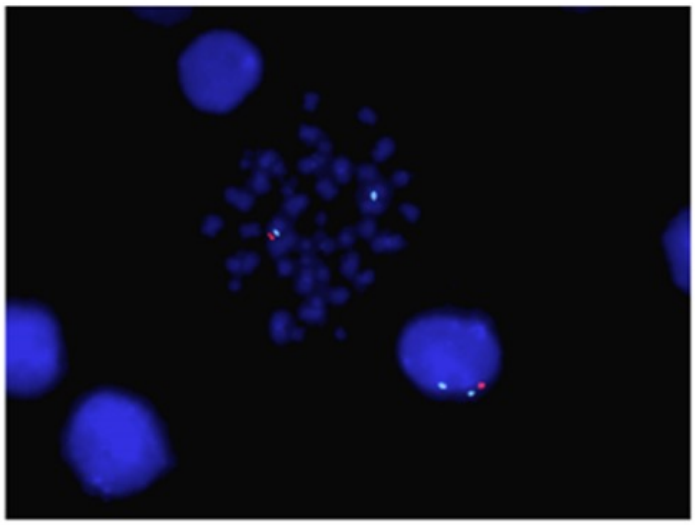
DISCUSSION

The SRY gene localized on the Y chromosome is responsible for the testicular determining factor (TDF), and this factor constitutes the most important step in sex development. [6] In 46 XX male syndromes, 90% of patients have Y chromosomal material, including the SRY gene. It is stated that this material is located at the end of the short arm of the paternal X chromosome by Y-X translocation during meiosis. [7] The presence of the SRY gene is responsible for the formation of the masculine phenotype; Indeed, ambiguous genitalia appears more frequently in 46 XX male syndrome without Y chromosome material and SRY gene. [8] Although this is the most frequently discussed theory, there may be an X-linked somatic mutation responsible for testicular differentiation or a Y mosaicism found only in the gonads. [8] It is thought that the SOX-[9]



Karyotip: 46,XX

Fig. 1. The karyotype analyses of the patient



Karyotip: ish (DXZ1x2, DYZ1x0, SRYx1) [100]

Fig. 2. The FISH analyses show that SRY gene region is located on the chromoseome X. One orange (SRY) and two aqua (DXZ1) signasls were recognised.

gene is affected in X-linked mutations and this gene behaves like SRY. [9] There are AZF (Azoospermia factor) gene families responsible for azoospermia on the Y chromosome. Gene regions subdivided as AZFa, AZFb, AZFc and AZFd encode proteins responsible for sperm maturation. [10] AZF mutations are very common in patients with 46 XX testicular disorders. [11]

In the classical type, which includes 90% of the patients, there are usually no signs before puberty. Insufficient testicular development after puberty, gynecomastia, and adult infertility are the most common reasons for admission to the hospital. The phenotypes of the patients are masculine with adequate terminal hair growth, as in our case. Testicles are usually less than 5 ml, hypospadias or undescended testicles can be seen in a few of them. All are infertile. Breast ultrasonography is compatible with gynecomastia. [5] SRY is negative in 10% of patients and these patients may have ambiguous genitalia. Patients are at risk of osteopenia/osteoporosis and low muscle mass due to hypogonadism. They also suffer from erectile dysfunction. Psychiatric comorbidities are common. [12]

The diagnosis of the disease can be made by clinical, laboratory and cytogenetic studies. Hypergonadotropic hypogonadism predominates in the laboratory. After puberty, testosterone is low and serum FSH and LH are high. 11 In 90% of these patients with 46 XX in cytogenetic analysis, the SRY gene is found to be positive by FISH or PCR. [8] AZF mutations are common.

Testosterone replacement should be given in cases with clinical and laboratory androgen deficiency. Testosterone replacement can be started from puberty. Patients should also be investigated for osteoporosis and closely monitored for testosterone side effects. Surgery may be recommended in cases with external genital anomalies or severe gynecomastia. Every diagnosed patient should be given psychosocial support. [9]

CONCLUSION

We diagnosed the patient who applied to our outpatient clinic with gynecomastia, as a result of laboratory and genetic examinations, with “De La Chapelle Syndrome”. We started testosterone replacement therapy, referred for psychological support and scanned for osteoporosis. Although De La Chapelle Syndrome is a very rare syndrome, it should be kept in mind in men with infertility or gynecomastia and genetic consultation should be requested in appropriate patients.

Authors’ Contribution

Study Conception: MCŞ, İE, NHE, SC, FD, AY; Study Design: MCŞ, İE, NHE, SC, FD, AY; Supervision: MCŞ, İE, NHE, SC, FD, AY; Materials: MCŞ, İE, NHE, SC, FD, AY; Data Collection and/or Processing: MCŞ, İE, NHE, SC, FD, AY; Statistical Analysis and/or Data Interpretation: MCŞ, İE, NHE, SC, FD, AY; Literature Review: MCŞ, İE, NHE, SC, FD, AY; Manuscript Preparation: MCŞ, İE, NHE, SC, FD, AY and Critical Review: MCŞ, İE, NHE, SC, FD, AY.

Conflict of interest

None to declare.

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