Case report

A CASE OF FAMILIAL MALE-LIMITED PRECOCIOUS PUBERTY WITH MUTATION OF (LHCGR) GENE, Peru EXPERIENCE

ABSTRACT:

Aims To describe a case of familial male-limited precocious puberty (FMPP) that has been responding well to therapy with non-steroidal antiandrogen (bicalutamide), third-generation non-steroidal aromatase inhibitors letrozole - anastrozole and triptorelin.

Presentation of Case We present a 5-years old, male child with FMPP, due to mutation in the luteinizing hormone/chorionic gonadotropin receptor LHCGR gene who presented with precocious puberty. We describe his clinical and biochemical response to treatment after 41 months of follow-up.

Discussion and Conclusion FMPP, also known as testotoxicosis, is a rare cause of precocious puberty in males that is still being studied. It is caused by a mutation in LHCGR gene, resulting in the receptor being constitutively activated. This causes excessive production of testosterone, leading to precocious puberty in males. Therapy is aimed to decrease the effects of testosterone, as well as stopping the conversion of testosterone to estrogen, in this direction using bicalutamide and anastrozole have been promising. No therapy guidelines have been established for this condition. Because of the limited number of reported cases, small sample sizes, and short-term outcomes. In this case report contributes with favorable findings, regarding the use of antiandrogen therapy and third-generation aromatase inhibitors in the treatment of FMPP and highlights on the importance of monitoring growth. Also adds to the literature by demonstrating a (LHCGTR) receptor gene mutation that responded well to a combination of bicalutamide and anastrozole.

Keywords: Familial male limited precocious puberty, testotoxicosis, non-steroidal aromatase inhibitor, bicalutamide, bone age, short stature, adult height.

INTRODUCTION

Testotoxicosis or familial precocious puberty limited to men (FMPP) is a is a very rare cause of precocious puberty seen exclusively in males, described 36 years ago by Schedewie HK and collaborators [1]. An activating mutation in the LHCGR may occur de novo, but it is usually inherited as an autosomal dominant pattern. It is caused by a constitutively activating mutation of the luteinizing hormone (LH)/choriogonadotrophin receptor gene (LHCGR), located on the short arm of chromosome 2 [2,3,4,5], G protein-coupled receptor [6], which under normal conditions is activated by LH and human chorionic gonadotrophin (hCG), while in the absence of the hormonal ligand promotes the production of cAMP resulting in the autonomous stimulation of Leydig cells and increased production of androgens in pre-pubertal stage [1,2].

The LHCGR mutations are mainly found in exon 11 [5-7] and only affects males while females are carriers, perhaps because they require the hormonal synthesis of both LH and follicle stimulating hormone (FSH), and because the activation of the LH receptor (LHR) alone would not cause symptoms [2] or that the degree of dysfunction is simply not high enough to cause symptoms [7]. Testicular histology shows hyperplasia of the Leydig cells [8] while the biochemical characteristics are pubertal testosterone levels in the presence of pre-pubertal gonadotropin levels [1].

The signs of puberty usually occur between 2 to 4 years of age with an increase of growth rate (GR), progressive virilization, acne, acceleration of bone maturation (due to the conversion of androgens to estrogens by the aromatase enzyme), which causes premature epiphyseal closure and affects negatively the final height [9]. FMPP can cause activation of the hypothalamic-pituitary-gonadal (HPG) axis and the onset of central precocious puberty and the risk of developing oligospermia and infertility in adult life [10].

There are few reports on the final height in FMPP; and although there is no therapeutic consensus, recent reports show favorable results with the use of bicalutamide and anastrozole [11,12].

The current report describes a case of FMPP that has been responding well to therapy with bicalutamide, letrozole - anastrozole and triptorelin (an GnRH analog).

CASE PRESENTATION

Our case is a 4-years-10months-old male who presented to our hospital, the parents noticed, that he was aggressiveness, accelerated linear growth and increase in penis size from 4 years of age, with axillary odor. He was a product of cesarean section, with a birth weight 3270 gr, length 50 cm and head circumference 34.5 cm. He was the first –born child for the family with normal psychomotor development, history of chickenpox encephalitis at 4-years-old that resolved without complications and the child’s parents refer negative history

of exposure to creams, gels, or medications containing testosterone and consanguinity negative also for similar condition.

Physical examination revealed: weight 22.6kg (95p, +1.7DS), height 118.3cm (+2.08 DS); and BMI 16.1kg/m2 (0.68 DS). The paternal height was 165.8cm and maternal height of 149.5cm with an expected final height of 164.3 (± 6.5 cm). Facial acne; penis 7 x 3 cm (90th percentile for age); Tanner stage II (G2 - testicular volume 6 mL bilateral and VP3) and no evidence of café-au-lait skin macules.

Laboratory tests and references values (In parenthesis) showed the following results: LH 0.1mU/mL (0.1–1.1), FSH 0.4mU/mL (0.3–3.8), testosterone 375ng/dL (2.0–25), dehydroepiandrosterone sulfate (DHEA-S) 82µg/dL (5–194), androstenedione 11ng/dl (5–51), 17-OH progesterone 0.74ng/dL (0.1–4.0), TSH 3.74mUI/ml (0.3–6.7), free T4 1.28 ng/dl (8.4–29.6) and cortisol (am) 8ug/dl (0.6–24) and ACTH stimulation test was not performed. The response to the LHRH stimulated test was LH (basal = 0.1mU/mL and post = 2mU/mL), FSH (basal = 0.2mU/mL and post = 1.4mU/mL), with a basal LH/FSH ratio of 0.5 and after stimulation of 1.4. The bone age (BA) was 8.9 years and the bone age/chronological age ratio (BA/CA) was 1.75. X-rays of the skull, spine and long bones were normal. The findings of pituitary magnetic resonance imaging pointed out Rathke's cleft cyst. Considering central precocious puberty (CPP) of peripheral onset, he started treatment with triptorelin at a dose of 3.75 mg/ intramuscular every 28 days.

The patient returned 4 months later, showing G3 (bilateral VT 8cc) and VP4; and laboratory test results showing: human alpha-feto-protein (AFP) 1.15ng/ml, carcinoembryonic antigen (CEA) 2.15ng/ml, hCG < 0.1mIU/ml, liver function, normal lipid profile, and normal testicles sonography. The case was reevaluated, raising the possibility of FMPP; triptorelin is suspended and letrozole is started at a dose of 2.5 mg /day orally. Genetic examination revealed: LH-GCR genotype with a pathogenic variant in exon11, C617Y, confirming diagnosis of FMPP. New test with LHRH shows: LH (post 60'= 5.2mIU/ml, post 90'= 4.0mIU/ml) and FSH (post 60'= 1.9mIU/ml, FSH post 90´= 1.7mIU/ml).

At the age of 5-years-6 months-old, started treatment with bicalutamide (50 mg/ day orally), continued with letrozole (2.5 mg/day orally) and restarted triptorelin (3.75 mg intramuscular every 28 days); treatment that followed for 31 months changing from letrozole to anastrozole 1 mg /day orally (because it was the drug available in our hospital) to date. The findings of the clinical and laboratory response under treatment are shown in Table 1.

Table 1. Clinical, laboratory and imaging response to the treatment of the patient with FMPP

Time (months)	Height cm (DS)	IMC (Kg/T^2)	Testicular volumen (ml) / pubic	Bone age (TW2)	LH (mUI/mL)	FSH (mUI/ mL)	Testosterone (nmol/L)	RX Spine	AFP (nmol /L)	CEA (nmol /L)

			hair							
0	126 (2.75)	15.7 (0.36)	VT = 8 VP = 2	8.9 *	0.1	0.6	12.8	----	3.9	7.6
6	128.2 (2.5)	15.9 (0.46)	VT = 6-8 VP = 2	10	0.3	0.3	7.7	----	3.1	10.3
13	131 (2.29)	16 (0.44)	VT = 6-8 VP = 2		0.31	< 0.1	2.3	Normal	4.8	4.8
25	135.5 (1.88)	16.2 (0.36)	VT = 6-8 VP = 2	10.7	0.4	0.16	3.7	Normal	----	----
31	136.5 (1.56)	15.8 (0.05)	VT = 6-8 VP = 2	11.0	0.33	< 0.1	6.9	Normal	----	----
41	139.9	15.6	VT = 6-8 VP = 3	11.6	0.44	0.12	0.0001**	Normal	-----	----
*Bone age taken 4 months prior to the start of the combined treatment of bicalutamide, letrozole and triptorelin **Free testosterone										

The patient has had adequate adherence and tolerance to the treatment, without side effects, with a significant improvement in his linear growth, bone maturation and prediction of final height (see Figures 1 and 2). The ratio of BA/CA has decreased from 1.75 at the start of treatment to 1.3 years to date.

DISCUSSION

The FMPP is the result of an autosomal dominant disorder linked to the X chromosome, however, there may be sporadic cases like that of our patient having a mutation, like the one described in 2010 by Nagasaki K, et al. in an 8-year-old Japanese child [5] (fig.3), and constitutes to the best of our knowledge the first case demonstrated in our institution; unlike them, we did not have the opportunity to identify the mutation in the mother, but there was no positive family history, which makes us presume this is a de novo mutation. As Schedewie HK [1] and Schoelwer M [10] have described on FMPP, in our patient the development of secondary sexual characteristics before 4 years of age, advanced BA, and the difference between penile growth and testicular volume in stage II of Tanner led to clinical assumption of peripheral precocious puberty and added to the biochemical findings that showed a disproportion between the levels of gonadotrophins and testosterone.

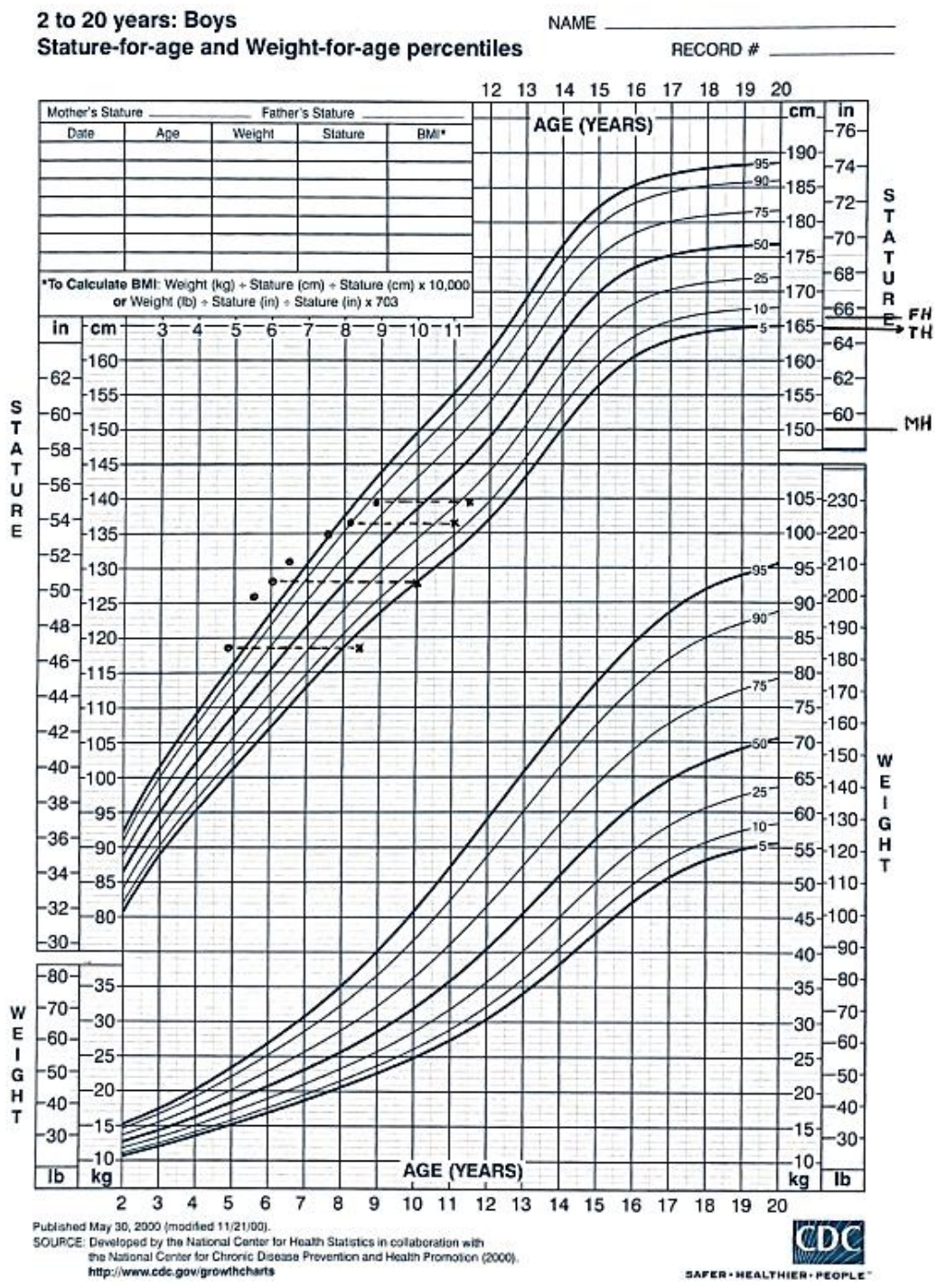
In FMPP, the main therapeutic goals include slowing the progression of virilization and epiphyseal maturation. To achieve the first goal therapy would include either blocking the peripheral actions of testosterone at the androgen receptor or inhibiting the synthesis of testosterone while the second therapeutic goal would be achieved blocking the action of estrogens at the epiphyses or blocking the aromatization of testosterone to estradiol [10-12]. In our case, we chose the combination of the selective non-steroidal antiandrogen bicalutamide (binds to androgen receptors and prevents the action of dihydrotestosterone and testosterone on target cells) at a dose of 2 mg/Kg/day (50 mg/day orally) extrapolated from the usual dose used for prostate cancer in adults and previously reported by Reiter EO [11] and Kreher NC [12], associated with letrozole and subsequently anastrozole, third-generation non-steroidal aromatase inhibitors (fig.3), which blocks the biosynthesis of estradiol and

which has been used to improve short stature in men or delay bone maturation in patients with congenital adrenal hyperplasia, having demonstrated good safety only with discrete morphological changes of the vertebrae in the long term with the use of letrozole [13,14].

As reported by Nagasaki K [5], Kreher NC [12], Leschek EW [15], Lane LC [16] and Kor Y [17], our patient also developed central precocious puberty secondary to prolonged exposure of the hypothalamus to high levels of sex steroids, so the GnRH analogue triptorelin had to be added. During the treatment, the BA has progressed slowly and the prediction of his final height has improved from 163 cm at the beginning to 170 cm at the end of this last evaluation, placing him in the upper range of his target height (figure 1, 2), showing like Kreher NC [12], Leschek EW [15] and Lane LC [16] the achievement of this objective [12]. The changes in their sexual characteristics have not progressed with the maintenance of the therapy associated with the GnRH analogue and in addition, other favorable changes have been a decrease in aggressive behavior and acne, observations also reported with this treatment by Reiter EO [11], Kreher NC [12] Leschek EW [15] and Mitre N [18].

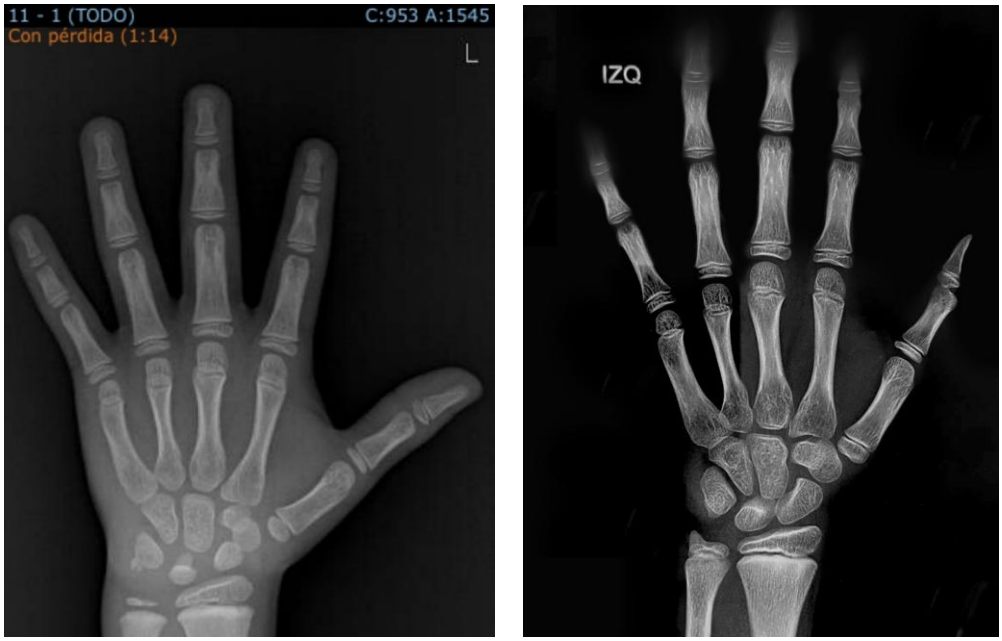
Regarding side effects, by blocking brain androgen receptors, bicalutamide causes an increase in the concentration of testosterone and altered negative feedback at the hypothalamic-pituitary level [18], which could explain the high levels of testosterone observed in the previous controls of our patient while that letrozole could produce alterations in the vertebrae [16], which have not been observed in our patient (figure 4), and triptorelin, as described in large series on the management of central precocious puberty, has also shown great safety in our patient [19].

Conclusion: FMPP is a rare disorder that is still being studied. No therapy guidelines have been established for this condition. Because of the limited number of reported cases, small sample sizes, and short-term outcomes. However, this case report contributes with favorable findings, regarding the use of antiandrogen therapy and third-generation aromatase inhibitors in the treatment of FMPP and highlights on the importance of monitoring growth. Also adds to the literature by demonstrating a (LHCGTR) receptor gene mutation that responded well to a combination of bicalutamide and anastrozole.



(●)= chronological age; X = bone age; FH= father's height; MH= mother's height; TH=target height

Figure 1. Height growth chart, showing progression of chronological age and bone age.



Left: AC= 4-years-10 months-old Right: AC= 8-years -10 months-old

Figure 2. Comparison of bone age at the start of treatment and at the last control

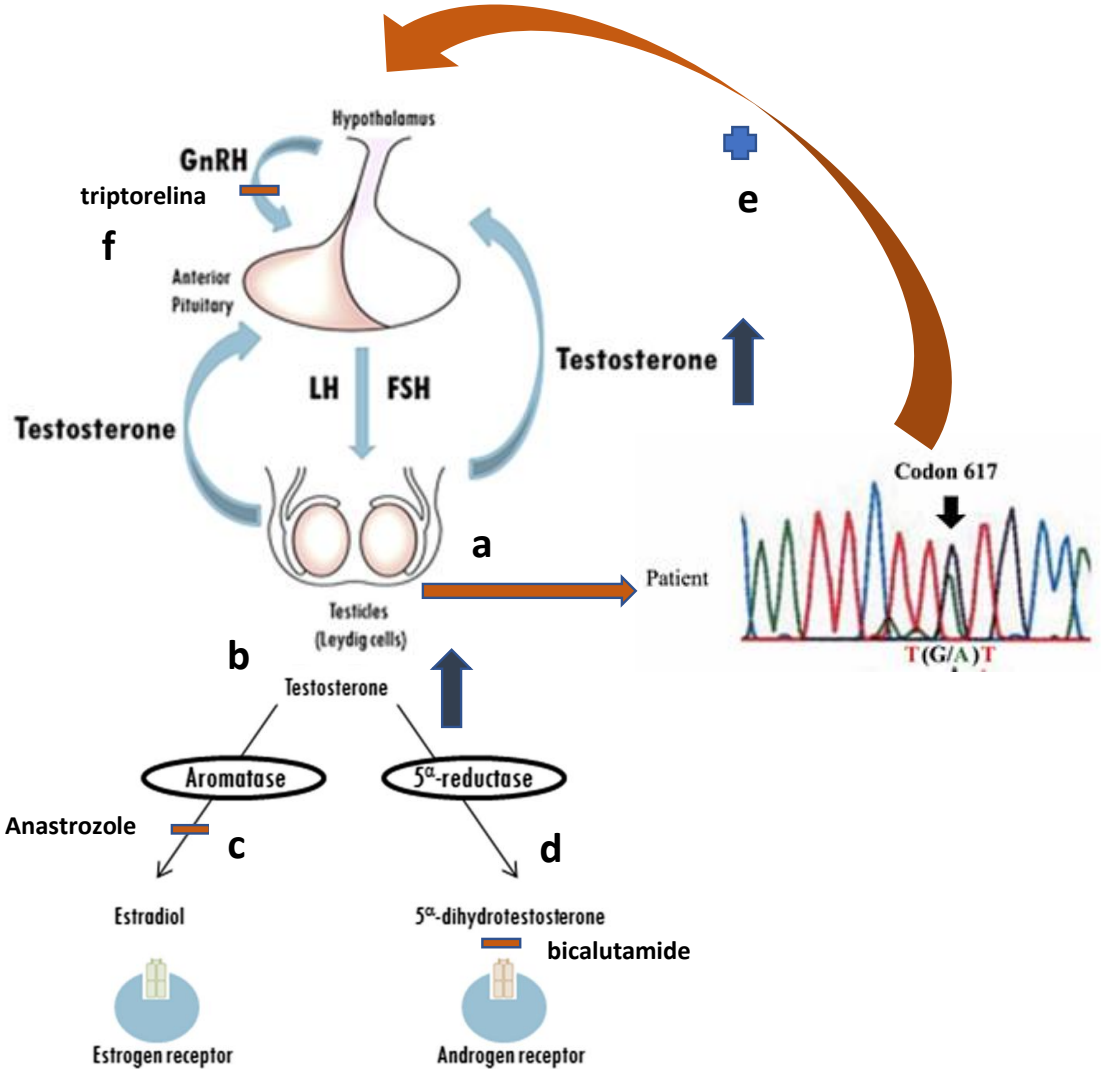
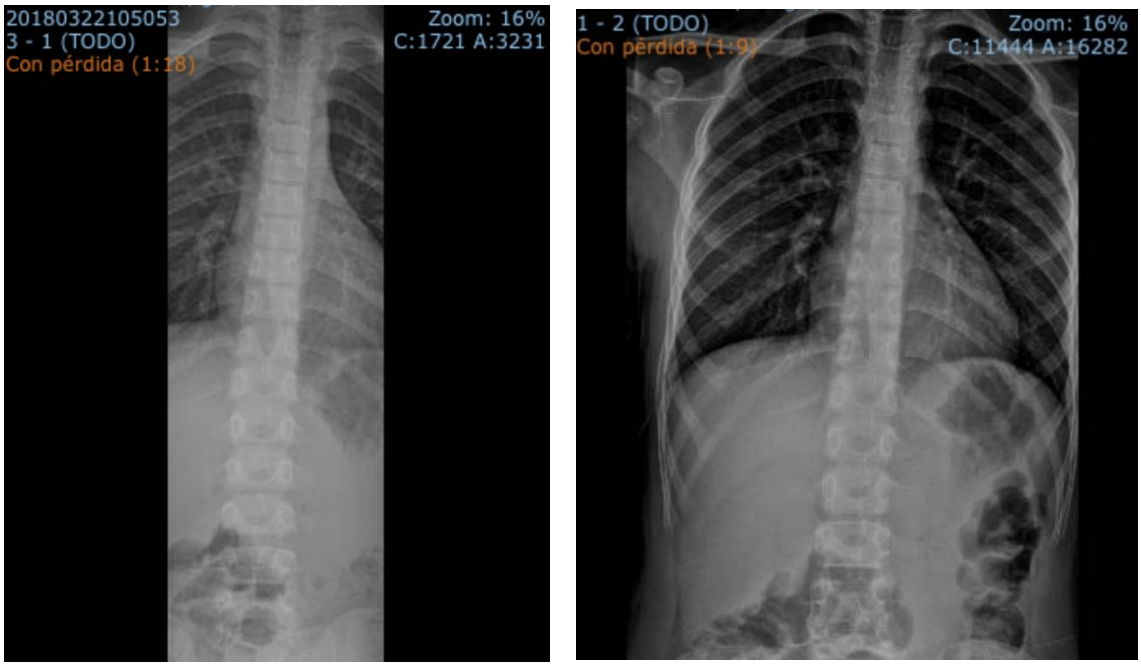


Figure 3. HPG axis diagram, showing site of mutation and action points of drugs used in treatment. a. Electrochromatogram showing a heterozygous mutation (c.1850G>A, p.C617Y) (image taken of reference [5]), b. increased testosterone production, c. aromatase inhibitory action of anastrozole, d. bicalutamide blocking action, e. prolonged action of sex steroids on the hypothalamus, f. inhibitory action of triptorelin



Left: start of treatment Right: last control.

Figure 4. Comparison of Spinal X-rays at the start of treatment and at the last control

DATA AVAILABILITY

The data is recorded in the institutional clinical history and is protected according to the regulations of the research ethics committee of our hospital.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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