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Testicular Microlithiasis as a cause of unresponsive treatment in a hypogonadal boy suspected of Kallmann Syndrome

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Abstract :
Background : Puberty is a critical period where there were a series of dramatic changes in physical and hormonal resulting in sexual maturity. There are various reproductive problems appearing during puberty, one of which is Kallmann syndrome (KS) with a prevalence of 1:48.000.
Clinical case: We reported a case of a 17-year-old boy reporting no signs of puberty. Physical examination was carried out with several findings including accumulation of abdominal fat, anosmia, presented a high-pitched voice, and no secondary sexual characteristics. Hormonal assay was conducted and showed a results of testosterone 0.2 nmol/L, estradiol <5 pg/mL, FSH 0.1 mIU/mL, and LH <0.1 IU/L and diagnosed with suspect of KS. The patient received an injection of hCG 250 micrograms/injection once a week for 4 weeks and no clinical improvement based on physical examination. Ultrasound examination showed the results of grade III varicocele in the left testis and microlithiasis in both of the testis. Patient then received testosterone therapy (Sustanon 250 injection) once a week for 4 weeks and showed several improvements in the sign of puberty.
Conclusion: Testosterone therapy as follow-up therapy in a boy with delayed puberty and suspected KS showed a result of developed good condition of virilization.

Keywords - *Delayed puberty, Kallmann syndrome, Varicocele, Testicular microlithiasis, Hypogonadotropic hypogonadism, Testosterone therapy*

I. INTRODUCTION

Puberty is a critical period in the process of growth and development from childhood to adulthood. Physical and hormonal changes occur during this period resulting in sexual maturity. Puberty in boys is characterized by an increase in testicular volume greater than 4 mL and testicular enlargement greater than 2.5 cm in length at the age of 9.5-14 years [1, 2]. Delay in the maturation of the hypothalamic-pituitary-gonadal (HPG) axis will cause hypogonadotropic hypothalamic conditions, it is a condition of gonadotropin-releasing hormone (GnRH) deficiency, which causes a decrease in the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in decreased testosterone production [3]. Delayed puberty is one of the abnormal conditions at puberty which is characterized by the absence of testicular enlargement at the age of ≤ 14 years [2]. The most common cause of delayed puberty in males is a decrease in the tempo of growth known as constitutional delay of puberty and growth (CDPG). A number of 53% of adolescents aged 18 years affected by CDPG, with more frequency in males (63%) than females (30%) [4].

One of rare pediatric genetic problem which is often associated with the pubertal period is Kallmann syndrome (KS). Research in Finland showed the prevalence of KS at 1:48.000 with a very large difference in men (1:30.000) and women (1:125.000). It is a form of congenital hypogonadotropic hypogonadism (CHH) characterized by hyposmia or anosmia. Low levels of GnRH lead to the insufficiency of sex steroid hormone resulting in the disturbance of sexual maturity and failure in the development of secondary sexual characteristics [5]. The diagnosis of KS is made through evaluation of congenital hypogonadotropic hypogonadism condition, anosmia, history of cryptorchidism and/or micropenis, absence of secondary sexual characteristics, decreased libido, and infertility [6, 7]. Hormonal examination, brain imaging, and genetic testing also need to be carried out for the diagnosis of KS [8].

Various problems in the reproductive organs can occur in the process of male genital development during the pubertal period, one of them is varicocele. This condition is manifested by abnormalities in the results of the sperm parameters examination [9, 10]. One European study conducted on 7000 young men with an average age of 19 years showed 15.7% of varicocele cases [11]. Meanwhile, another study showed that from 4,052 Turkish children and adolescents, there was a varicocele prevalence of 0.8% in boys aged 2-6 years, 1% in boys aged 7-10 years, 7.8% in boys aged 11-14 years, and 14.1% in boys ages 15-19 years. These results indicate an increase in prevalence along with puberty in boys [12].

Another condition associated with male genital development disturbance is the presence of testicular microlithiasis (TM), a condition that is generally rare and is detected incidentally on ultrasound examination of the scrotum. Based on the ultrasound examination, the TM appearance was identified with multiple small, same-sized echogenic non-shadowing foci that can be observed throughout the testicle [13]. A retrospective study of 3370 patients under 18 years of age by Cooper et al. showed that 83 (2%) identified the presence of TM through ultrasound examination with the most frequent indication being scrotal pain (40 of 83 patients, 48%) [14]. This paper presents a case report of delayed puberty in a boy with the multiple problems: suspected Kallmann syndrome, varicocele, and testicular microlithiasis, and to provide an information of its management and treatment.

II. CLINICAL CASE

A 17-year-old boy came to our andrology outpatient clinic reporting no signs of puberty. A physical examination has been carried out with the results of no indication of gynecomastia, presented a eunuchoid posture with accumulation of abdominal fat, anosmia, presented a high-pitched voice, and no secondary sexual characteristics were found. The patient's weight 76 kg, height 174 cm, and a body mass index of 25.1 were categorized as overweight according to the Indonesian Ministry of Health. Patient reported have no experienced in nocturnal emission. Based on the genitalia examination, it was observed no pubic hair with a couple of testicles in the right and left scrotum, tecticular volume was <2 mL and presents a microphallus with a penile length of 3-4 cm. The first hormonal examination showed a results of testosterone 0.2 nmol/L, estradiol <5 pg/mL, FSH 0.1 mIU/mL, and LH <0.1 IU/L. Based on the results of the physical and hormonal examination, the patient was diagnosed with suspected Kallmann syndrome.

Treatment begins with giving an injection of human chorionic gonadotropin (hCG) (OVIDREL®) 250 micrograms/injection once a week for 4 weeks which aims to stimulate testosterone production. This treatment was evaluated through the second testosterone hormonal examination after four injections with the result of 0.86 nmol/L. Based on the testosterone examination result, the patient then administered hCG injection combined with clomiphene citrate and was evaluated through the third hormonal examination with the following results: testosterone 1.87 nmol/L, estradiol 18.32 pg/mL, and FSH 0.1 mIU/mL. Physical examination was performed after 4 weeks of therapy but showed no clinical improvement. Changes in penile length, testicular volume, and pubic hair growth were not identified. So that it is necessary to carry out additional examinations regarding the absence of a response to treatment.

Ultrasound examination of the testes identified the size of the right testicle 1.36 x 0.75 x 1.38 cm and the size of the left testicle 1.75 x 0.84 x 1.54 cm. There is testicular atrophy with bilateral testicular microlithiasis (Fig. 1). On the right testicle, multiple homogeneous hyperechoic lesions were seen scattered in the periphery of the testicular parenchyma, measuring 0.6 mm in diameter with less than 10 pieces. Meanwhile, on the left testicle, there were multiple homogeneous hyperechoic lesions scattered in the peripheral area of the

testicular parenchyma, with a diameter of 0.8 mm, the number of which was less than 10. Grade III varicocele was identified in the left testis (Fig. 2).

The patient had undergone left varicocele surgery, and subsequently received testosterone therapy (Sustanon 250 injection) once a week for 4 weeks. Physical examination after testosterone therapy was shown the result of the growth of body hair, pubic hair, and penile erection size was 12 cm, but there is no change in testicular volume. The patient also stated that there is an increase in the frequency of morning erections and has experienced a nocturnal emission.

III. DISCUSSION

This case is a congenital hypogonadotropic hypogonadism (CHH) case that does not respond to treatment reflected by no physical changes after injection of human chorionic gonadotropin (hCG) during four weeks. Congenital hypogonadotropic hypogonadism (CHH) is a rare condition resulting from low GnRH secretion. Hormonal examination in CHH showed low plasma FSH and LH levels accompanied by decreased levels of sex steroid hormones. CHH condition accompanied by a decreased sense of smell is the main character that appears in Kallmann Syndrome (KS) [6, 15]. This case management was carried out according to the guidelines in the European Consensus Statement on congenital hypogonadotropic hypogonadism [16]. KS is characterized by the lack of sexual maturation during the puberty period including delayed testicular development, lack of pubic hair, and a little case of micropenis. This condition is correlated with the low levels of LH and FSH which in turn causes low levels of testosterone [5, 16]. The hypogonadotropic hypogonadism (HH) condition in this patient is expected to respond to the treatment using hCG in order to stimulate endogenous testosterone production. Administration of hCG in KS management has been carried out in a previous case report by Pierzchlewska et al. who stated that giving hCG to KS patients with hypogonadotropic hypogonadism can increase pubertal development and gonadal function, indicated its more beneficial effects than testosterone replacement therapy [17].

The administration of hCG therapy in this patient did not show a positive response, so it needs to be evaluated and considered for another therapy strategy. Several therapies are suggested to be used in the management of hypogonadism cases, including human chorionic gonadotropin (hCG), aromatase inhibitors, and selective estrogen/androgen receptor modulators (SERMS and SARMS) [18-20]. This therapy is recommended considering several reports of an increase in cases of subfertility in the administration of testosterone therapy (TTh) as the main choice in the treatment of hypogonadism. This side effect is caused by a decrease in endogenous testosterone production due to negative feedback [21, 22].

We then administered hCG combined with clomiphene citrate (CC) to the patient, as known that CC is one of the types of selective estrogen/androgen receptor modulators which can bind to estrogen receptors in the hypothalamus and pituitary, thereby blocking the binding of estrogen to its receptors. This mechanism of action results in an increase in gonadotropin release and leads to an increase in testosterone production [23]. The results of the evaluation of combination therapy with hCG and CC showed no changes in penile length, testicular volume, pubic hair growth, and only a slight increase in testosterone levels. Then we consider giving testosterone therapy (Sustanon 250) which is known as one of the therapies in the management of KS. Sustanon is one of the anabolic–androgenic steroids (AAS) administered by injection that induces a continuous secretion of testosterone. Delayed puberty and hypogonadotropic hypogonadism are two conditions indicate for Sustanon injection therapy based on Food and Drug Administration (FDA) recommendations [24, 25]. The patient received Sustanon injection once a week for 4 weeks and from the evaluation results are identified growth of body and pubic hair, penile erection length was 12 cm, but there is no change in testicular volume.

Testosterone therapy can be used in cases of KS following previous hCG therapy, as done by Pierzchlewska et al. in male patients with no signs of puberty and a diagnosis of KS. Administration of hCG injection followed by testosterone replacement therapy give satisfactory results with the development of signs of puberty and achievement of virilization. There was a reversal of the condition of hypogonadism even though the treatment had been carried out for 2 years. This shows that the administration of testosterone is considered to be able to maintain virilization conditions in KS [17].

Testosterone therapy was given for 12 weeks, and based on evaluation examination it was observed that there was a good condition of virilization. The results of previous studies showed that only 10-20% of KS

patients showed spontaneous improvement of reproductive function after hormonal replacement therapy [26, 27]. However, testosterone therapy is necessary to improve quality of life, sexual function, and also muscle and bone function [28, 29]. In this patient, sexual function was greatly improved as evidenced by the increased frequency of morning erections and having experienced nocturnal emission. However, there is a possibility of experiencing infertility due to the absence of an increase in testicular volume after the administration of testosterone therapy. This patient did not undergo a genetic diagnosis examination due to the lack of access to this examination in our country, so the diagnosis of KS was only based on the hypogonadotropic hypogonadism condition, patient's eunuchoid posture, and anosmia.

Based on the patient's testicular ultrasound examination, it is identified a grade III varicocele in the left testis. The degree of varicocele varies, ranging from subclinical to grade III based on its severity. Subclinical varicoceles can only be identified by ultrasound examination. In grade I, varicocele is palpable with Valsalva, grade II can be observed with Valsalva pressure and palpable without Valsalva pressure, while grade III can be observed with Valsalva pressure and palpable without Valsalva pressure and correlated with the "bag of worm" appearance [30]. Varicocele can increase oxidative stress and result in decreased testicular function in men which can disrupt spermatogenesis and subsequently will affect men's fertility status [31]. Varicoceles generally have normal or high levels of FSH and low levels of testosterone, but in this case, hypogonadotropic hypogonadism was found due to the dominant KS condition. There were no studies showing the prevalence of varicocele in KS, but there was a case report of Kallmann syndrome accompanied by grade III varicoceles by Tahi et al. in 28-year-old males who experience pubertal development disturbances [32].

Testicular damage from varicoceles has been reported. Liu et al. conducted a study to see the histological changes of the testes in rats model varicocele. The results showed bilateral testicular pathological changes, atrophy of the seminiferous tubules, and disturbance of spermatozoa development [33]. This patient had undergone varicocelectomy but no response to an increase in testicular volume was identified. One of the expected responses after varicocelectomy is an increase in testicular volume. A previous study by Badir et al. stated that adolescents with unilateral grade 2-3 varicocele who underwent varicocelectomy could experience catch-up growth of the testes up to 70%, and showed significant testicular growth [34].

Another finding of ultrasound examination is multiple homogeneous hyperechoic lesions less than 10 indicate the testicular microlithiasis condition. Testicular microlithiasis was categorized into limited testicular microlithiasis (LTM) with characteristic hyperechogenic spots <5 and classic testicular microlithiasis (CTM) with hyperechogenic spots ≥5 [35]. The number of hyperechogenic spots based on the patient's results of ultrasound examination was classified as CTM. The prevalence of TM in Kallmann syndrome is still unclear, but several studies have reported a case of TM in varicocele and hypogonadism conditions. Research conducted by Kocaoğlu et al. on 9 boys with a diagnosis of TM identified two children with a varicocele in the left testicle [36]. Previous studies stated that TM may be associated with several problems with the male reproductive system including testicular malignancy and hypogonadism [37]. A study conducted by O'Shaughnessy et al. stated that TM was identified in mice lacking endocrine stimulation. This was demonstrated by the presence of small amounts of microliths in 36% of the testes of hypogonadal mice which lack circulating gonadotropins [38]. In our case report, the patient did not show a positive response to hCG therapy. It is possible that conditions similar to those in animal studies were also experienced by our patients.

IV. FIGURES AND TABLES

A B

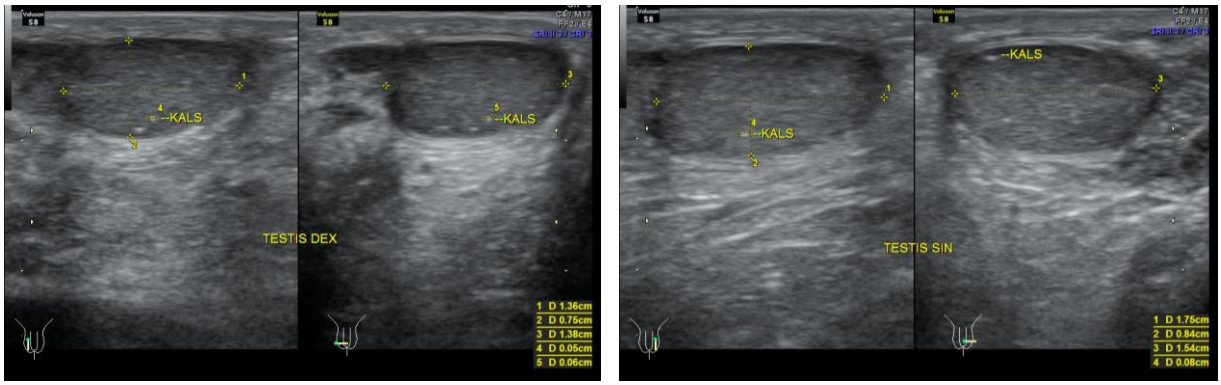

Figure 1. Microlithiasis identified in the right testicle (A) and left testicle (B)

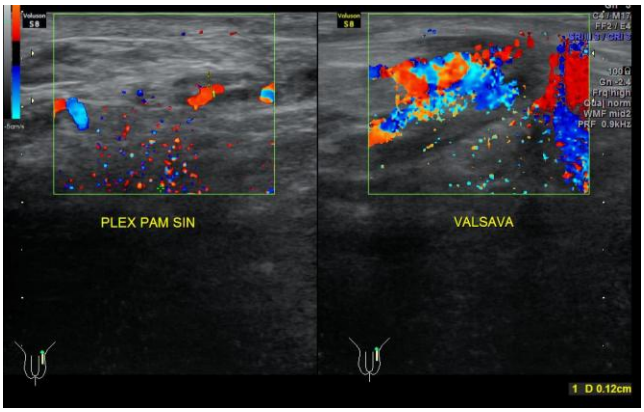

Figure 2. Grade III varicocele identified in the left testicle

V. CONCLUSION

In conclusion, our case has shown that the patient with delayed puberty with multiple abnormality: suspected Kallman syndrome, left varicocele, and bilateral testicular microlithiasis we treated did not respond to the hCG injection administration. Furthermore, we administered Testosterone therapy as follow-up therapy and noted that the patient had developed good condition of virilization.

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