UNEXPECTED OUTCOME IN A TREATED XY REVERSAL SYNDROME PATIENT

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SUMMARY – Hormone replacement therapy is mandatory to maintain quality of life and bone mineralization status in patients with gonadal dysgenesis. Occasionally, these patients need higher than recommended estrogen dosage to prevent signs and symptoms of hypoestrogenic state. Our 18-year-old female patient with XY sex reversal syndrome was gonadectomized and administered conventional hormone replacement therapy. Gonadoblastoma was found in the excised streak gonad. Five years after continuous replacement therapy, the patient reported unexpectedly hot flushes and amenorrhea in spite of regular hormone intake. Severe osteopenia was also detected. Unconventionally high estrogen dose was given with additional daily vitamin D and calcium supplement. Dual energy x-ray absorptiometry revealed lesser but evident osteopenia and the patient reported repeated bleeding without hot flushes on the new hormone regimen. Individualized dosage of estrogen is essential for these patients according to their bone status and subjective symptoms. Early therapy initiation along with continuous and frequent evaluation of bone status and quality of life is advised.

Key words: *XY sex reversal syndrome; Gonadoblastoma; Hormone replacement therapy; Osteopenia*

Introduction

The XY sex reversal syndrome, also called XY gonadal dysgenesis or Swyer syndrome, is a condition in which individuals with 46 XY karyotype in each cell have a female appearance. People with this disorder have female external genitalia and normal uterus and fallopian tubes. However, they do not have functional gonads (ovaries or testes). Instead, they have undeveloped gonadal tissue called streak gonads. Only 20% of all 46 XY pure gonadal dysgenesis are explained by a mutation or a deletion in SRY[1]. Variations of phenotypical appearance in these patients are described in the literature with or without evident background of the causing factor. Diagnostic procedure is well established and after confirmation of the syndrome hormone replacement therapy (HRT) is essential because of no gonadal estrogenic production. It is important to induce development of the breasts, the existing mullerian structures, inducing menstrual bleeding as well as reducing the risk of decrease in bone mineral density. Continuous therapy is advised to avoid estrogen withdrawal symptoms and negative effects on the life quality. The sooner the therapy begins the greater are the benefits for the patient. The incidence of gonad malignancy development in patients with gonadal dysgenesis is high, approximately 25%-30%[1]. The most common gonadal tumors in Swyer syndrome patients are gonadoblastoma and dysgerminoma. Therefore,

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laparoscopic gonadectomy is highly recommended as a standard prophylactic procedure. Although rarely reported in XY female patients, urinary tract anomalies are possible[1].

Case Report

We present a case of a young woman with Swyer syndrome after laparoscopic gonadectomy, who encountered several subjective and clinical difficulties after five years of continuous hormonal treatment. She got her menarche at the age of 15 and once a year had scant bleeding. The patient first visited her gynecologist at the age of 17 as she complained of cycle irregularities. Progesterone therapy induced light vaginal bleeding twice. At the age of 18, she visited our department because menstrual bleeding did not follow regular pattern as she was instructed. In the meantime, the patient developed hot flushes. The patient was 178 cm high, of athletic built, body weight 70 kg (body mass index (BMI) 22.1). She had developed breasts (Tanner 2/3), axillary and pubic hair (Tanner 3). Her external genitals were normally developed and *virgo*. Gonadotropin values were high (FSH 48.8 IU/L, LH 18.8 IU/L), estrogens were low (E2 0.05 nmol/L), HCG was negative, and the rest of hormonal laboratory findings were within the normal range. Transabdominal ultrasound showed small uterus (30x20 mm), a solid structure like ovarian tissue on the right side (1.8x1 cm) with no detectable ovarian tissue on the left side. Cytogenetic analysis showed 46 XY karyotype and positive SRY region on Y chromosome without mutations (PCR, FISH). After primary evaluation, the patient was informed and guided for the following procedures. The patient accepted psychological counseling started and continued during evaluation of her diagnosis at our hospital. Sequential HRT was prescribed immediately at the age of 18 (2 mg estradiol/1 mg norethisterone acetate; Trisequens®, Novo Nordisk), which eliminated hot flushes and induced regular menstrual bleedings. Several months later during diagnostic laparoscopy, a small uterus with both tubes and both streak gonads was visualized; biopsy showed connective tissue and ovarian stroma without follicles. Vaginal examination performed before the operation (the patient informed us that in the meantime she had been sexually active without any interference) revealed normal vagina and small cervix**.** Laparoscopic gonadectomy was performed with the patient's informed consent. Most parts of the gonadal streaks were firm connective tissue found between discrete areas of ovarian stroma, with rare and microscopically small inclusion cysts and psammoma bodies. There were no primary follicles. In the left gonadal streak, an accidental tumor was found, measuring 2 mm in diameter (Fig. 1a, b). Tumor nests were found to immunohistochemically stain positive for PLAP, CD117 and S-100, and

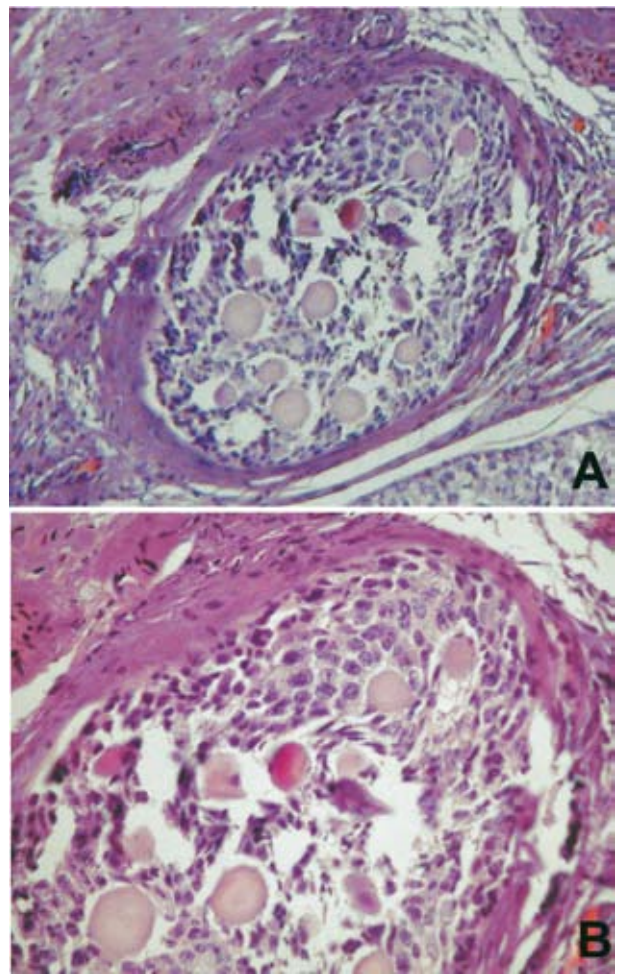

Fig. 1. Gonadoblastoma: (a) the tumor consisting of germ cells and sex cord derivatives in cellular nests surrounded by connective tissue stroma (HE, X100); (b) coronal pattern of sex cord derivatives along the periphery of the nests and surrounding small nests containing hyaline material; in-between, a mixture of cells (HE, X400).

negative for CEA, GFAP, desmin and CK MNF16 (Fig. 2a-c). According to morphological and immunohistochemical findings, the diagnosis of gonadoblastoma was made. The right gonadal streak showed no signs of tumor in ovarian and fibrous connective stroma. Intravenous urography showed no malformations of the urinary tract. Five years later, in spite of continuous hormonal therapy, hot flushes and amenorrhea developed. Vaginal ultrasound showed thin one-layered endometrium. The patient was eager to have regular bleeding. Additional laboratory endocrinological analysis revealed no other causes of this state. On thorough evaluation bone mineral density was evaluated as well. Severe osteopenia was detected and diagnosed by DEXA. Her hip neck T score was -1.64 and Z score -1.62, whereas lumbar spine T score was -2.45 and Z score -2.34. Commercially available monthly oral sequential combined estrogen-progesterone preparations were changed a few times for different progestins or different estrogen doses, without any impact on hot flushes or endometrial thickness until the three-month regimen of 3 mg estradiol (Estrofem®, Novo Nordisk) daily was introduced, opposed with 10 mg dydrogesterone (Dabroston®, Belupo) for the last 14 days. Furthermore, the patient was administered vitamin D (800 IU) and calcium (1000-1500 mg) daily. After a year of this therapy, osteopenia was less severe; hip neck T score was 1.6 and Z score -1.5, whereas lumbar spine T score was -2.1 and Z score -2.0. Later on, we reduced the estradiol daily dose to 2 mg and added gestagen every other month. The patient bled regularly and she was satisfied with her therapy and quality of life. Two years later, in the course of her check-up at our hospital, the patient reported scant but regular bleeding patterns without hot flushes. Transvaginal ultrasound scan showed unchanged uterus size (29x20x20 mm) with endometrium that was never thicker than 3 mm

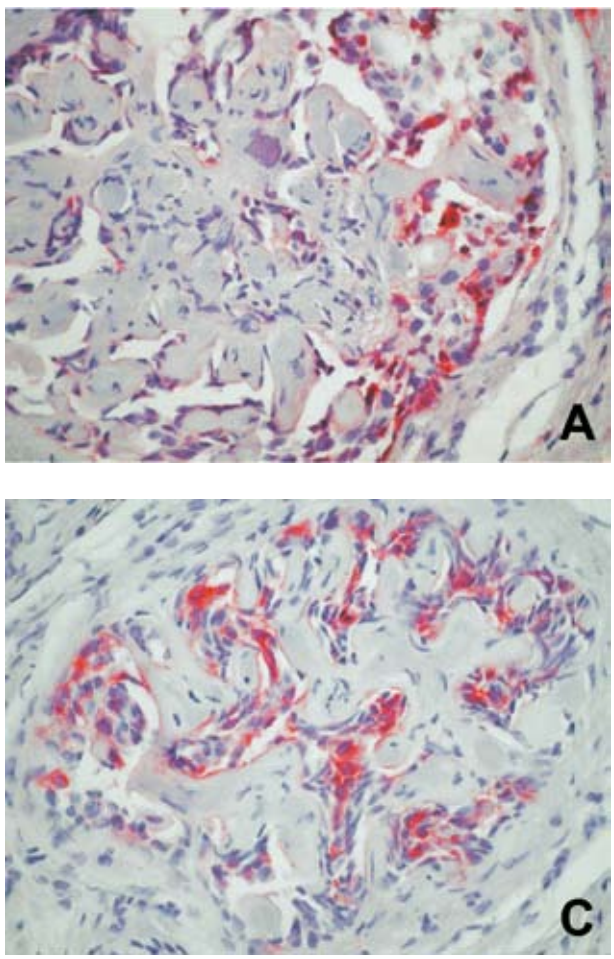

Fig. 2. Immunohistochemistry of the gonadoblastoma: (a) strong cytoplasmic reaction for PLAP was observed in tumor cells; (b) strong cytoplasmic and membrane reaction for CD117 was observed in tumor cells; (c) reaction for S-100 was found in tumor cell cytoplasm (X400).

in proliferative phase. Bone mineral density did not change. Osteopenia was still present with hip neck T score 1.8 and Z score -1.77, and lumbar spine T score -2.24 and Z score -2.17.

Discussion

The explanation for the developed breasts, spontaneous spotting and good early response to gestagen therapy in the patient's pubertal age is that there must have been some hormonal production by either some ovarian/gonadal tissue which degenerated prematurely or by peripheral conversion of androgens[2]. The patient experienced the first hot flushes in her teenage years, which are expected in patients with pure gonadal dysgenesis. Hot flushes were blocked by continuous sequential HRT, starting at age 18. The finding of unilateral gonadoblastoma on the surgery justified the procedure of gonadectomy.

Young women who develop symptoms of estrogen deficiency also lose bone[3]. The extent of bone loss in these women is directly proportional to the length of time without therapy[4]. Bone mineral density increases under estrogen influence beginning in the peripubertal period until around age 30[5]. Dual energy x-ray absorptiometry (DEXA) or bone densitometry is the standard method to measure bone mineral density. The spine and hip are usually measured. The World Health Organization established the criteria for determining T-score and Z-score. In our patient, osteopenia of lumbar spine and hip bone developed in spite of continuous HRT, suggesting her to be at a greater risk of fracture than young women of her age[5]. Bone mineral density (expressed as Z-score) of the spine was -2.34 and of the hip -1.62. Early teenage period is the time when the bulk of bone tissue is laid down under the influence of peak estrogen production and this development cannot be easily compensated later[6,7]. We believe that our patient started with HRT too late.

Later in life, the patient once again developed the signs of relative estrogen deficiency manifested as clinical signs and symptoms in spite of therapy. Therefore, at that time the patient needed greater exogenous dose of estrogen to stop hot flushes, to maintain endometrial proliferation and to enable bleedings. Her uterus size throughout the time of continuous therapy did not enlarge and stayed hypoplastic. We can only presume that the tissue sensitivity for exogenous estrogens might be lower in our patient[8]. Sudden appearance of hot flushes as well as severe osteopenia could be caused by the fact that the patient lost weight (8 kg) deliberately and decreased her BMI of 22 to 19, which is a reported and known risk factor for osteopenia[9]. Furthermore, resistant osteopenia in this case may also be the result of relative androgen deficiency, which can also compromise bone mineral density[10].

Conclusion

We found extremely important to ensure young XY reversal syndrome patients with additional psychological treatment to help them in developing self-esteem, sexuality and reaching right decisions during treatment. Psychological support ensured an enormous positive impact to our patient and helped her understand all suggested diagnostic, surgical and other medication treatments. An individualized therapeutic approach is mandatory in order to maintain their well-being, quality of life, and appropriate bone mineralization status[11]. Sometimes it is worthwhile to introduce higher than standard doses of estrogens, with vitamin D and calcium supplements. It is advisable to make more frequent search for symptoms of estrogen deprivation, as well as frequent check-ups of bone mineral loss. In our experience, there is a serious lack of relevant literature about resistance of this particular group of patients to conventional estrogen dose in replacement therapy. We did not find any literature data on bone mineral density in younger patients.

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Sažetak

NEOČEKIVANI ISHOD KOD LIJEČENE BOLESNICE S GONADNOM DISGENEZOM

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U bolesnica s disgenezom gonada liječenje hormonskom nadomjesnom terapijom potrebno je kako bi se očuvala kvaliteta života te primjerena mineralizacija koštanog tkiva. U liječenju je ponekad potrebno primijeniti višu dozu estrogena od preporučene kako bi se spriječili znaci i simptomi hipoestrogenemije. Prikazuje se osamnaestgodišnja bolesnica s čistom disgenezom gonada, liječena standardnom hormonskom nadomjesnom terapijom u koje je učinjena gonadektomija. Unutar fibrotičnog gonadnog tračka nađen je gonadoblastom. Bolesnica je liječena kontinuiranom hormonskom nadomjesnom terapijom pet godina, nakon čega je naglo razvila amenoreju te valove vrućine. Denzitometrijom se dokazala teška osteopenija. Bolesnica je potom liječena visokim dozama estrogena uz dodatak vitamina D i kalcija svakodnevno. Denzitometrijom se i dalje verificirala postojana osteopenija, ali manje izražena. Uspostavljena su redovita krvarenja bez valova vrućine tek uz tromjesečni režim hormonske terapije (estradiol 3 mg/3 mjeseca i didrogesteron 10 mg/posljednjih 14 dana). U bolesnica s čistom disgenezom gonada uputno je rano započeti s hormonskim liječenjem uza stalne i česte kontrole statusa koštanog tkiva i kvalitete života. Nužan je individualni pristup hormonskom nadomjesnom liječenju ovisno o subjektivnim smetnjama i statusu koštanog tkiva.

Ključne riječi: *XY poremećaji spola; Gonadoblastom; Hormonska nadomjesna terapija; Osteopenija*