A rare case of primary amenorrhoea and breast development in a 46,XY 15-year-old girl

Rzadki przypadek 15-letniej pacjentki z kariotypem 46,XY, pierwotnym brakiem menstruacji i prawidłowym rozwojem piersi

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Abstract

A disorder of sex development (DSD) is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. Swyer syndrome is an example of 46,XY DSD with a female phenotype. It usually becomes apparent in adolescence with delayed puberty and amenorrhoea. Spontaneous breast development is very rare. A 15-year-old girl was presented due to primary amenorrhoea with breast development compatible with Tanner stage V. Hormonal tests revealed hypergonadotropic hypogonadism with low level of oestradiol. Pelvic ultrasound and magnetic resonance imaging revealed a small uterus, and no ovaries were found. In the right lower abdomen, a structure of unknown origin was visible. The chromosome analysis revealed a 46,XY karyotype. The patient was qualified for a laparoscopic bilateral gonadectomy. Postoperative histopathological examination revealed gonadoblastoma. We underline the need to consider DSD 46,XY in the presence of primary amenorrhoea, even when pubertal development is present. Germ cell tumors have a tendency to grow and metastasize rapidly. Delayed diagnosis may increase the risk of malignant transformation and cause a poor diagnosis.

Key words: primary amenorrhoea, gonadal dysgenesis, Swyer syndrome, gonadoblastoma, disorder of sex development.

Streszczenie

Zaburzenia różnicowania płci polegają na niezgodności płci genetycznej i gonadalnej z fenotypem zewnętrznych narządów płciowych. Zespół Swyera jest przykładem DSD z kariotypem 46,XY i żeńskim fenotypem. Rozpoznanie jest ustalane głównie w wieku nastoletnim w związku z diagnozą pierwotnego braku menstruacji i opóźnionego pokwitania. Prawidłowy rozwój piersi występuje u tych pacjentek niezwykle rzadko. Piętnastoletnia dziewczyna została przyjęta w celu diagnostyki pierwotnego braku menstruacji. W badaniu fizykalnym rozwoj piersi wg skali Tannera oceniono na M5. W badaniach hormonalnych stwierdzono cechy hipogonadotropijnego hypogonadizmu z małym stężeniem estradiolu. W badaniu ultrasonograficznym i rezonansu magnetycznego miednicy małej zauważyono małą macicę, brak prawidłowych jajników. W podbrzuszu prawym widoczna była struktura niewiadomego pochodzenia. W badaniu cytogenetycznym stwierdzono kariotyp męski – 46,XY. Pacjentka została zakwalifikowana do zabiegu usunięcia gonad. W pooperacyjnym badaniu histopathologicznym stwierdzono gonadoblastomę. Prezentowany opis przypadku podkreśla konieczność wzięcia pod uwagę zespół Swyera w diagnostyce pierwotnego braku menstruacji, nawet w przypadku obecności drugorzędowych cech płciowych. Należy pamiętać, że nowotwory germinalne mogą szybko rosnąć i dawać przerzuty. Opóźnienie właściwego rozpoznania może zwiększać ryzyko zezłośliwienia nowotworu i niekorzystnie wpłynąć na rokowanie.

Key words: pierwotny brak miesiączki, zaburzenia różnicowania płci, dysgenezja gonad, gonadoblastoma, zespół Swyera.
Introduction

A disorder of sex development (DSD) is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical [1–3]. According to the Chicago classification, DSD is subdivided into three groups on the basis of cytogenetic, hormonal, gonadal histology, and clinical findings: 46,XY (primary disorder of testicular development or disorders in androgen synthesis or action), 46,XX (disorders of ovarian development, congenital adrenal hyperplasia, aromatase deficiency), and sex chromosome disorders (Klinefelter syndrome, Turner syndrome, chimerism, mixed gonadal dysgenesis) [1, 3, 4]. The overall rate of incidence is estimated at 1:4500 births, and that of DSD with Y chromosome material is approximately 1:20,000 births [4]. In patients with DSD the rate of associated congenital anomalies is significantly higher than in the general population. These abnormalities include small genital findings: 46,XY (primary disorder of testicular development or disorders in androgen synthesis or action), 46,XX (disorders of ovarian development, congenital adrenal hyperplasia, aromatase deficiency), and sex chromosome disorders (Klinefelter syndrome, Turner syndrome, chimerism, mixed gonadal dysgenesis) [1, 3, 4]. The overall rate of incidence is estimated at 1:4500 births, and that of DSD with Y chromosome material is approximately 1:20,000 births [4]. In patients with DSD the rate of associated congenital anomalies is significantly higher than in the general population. These abnormalities include small genitalia or other evidence of virilisation were observed. Laboratory findings revealed normal biochemistry. Hormonal tests were as follows: hypergonadotropic hypogonadism with low level of oestradiol and testosterone (follicle stimulating hormone 48.68 mIU/ml, luteinising hormone 25.79 mIU/ml, oestradiol 16.79 pg/ml [ranges shown in Table 1], testosterone 14.21 ng/dl [normal range: 6-86 ng/dl]). Pelvic ultrasound revealed a uterus that showed modest oestrogenisation, which was, however, insufficient to make the endometrium visible. No ovaries were found. In the projection of a right gonad a solid structure with a vague ultrasound image was found. To verify the results of the ultrasound examination, magnetic resonance imaging was performed – the uterus dimensions were appropriate for the age (6.0 × 1.8 × 3.2 cm). In the left gonad projection, a small structure with vesicles up to 3 mm was visible. The right gonad was not visible, while a 7 mm thick tissue lesion was found in that area. Fallopian tubes were present. In the right lower abdomen, a structure of unknown origin and with dimensions of 22 × 14 × 15 mm was visible. In the course of further diagnostic tests, the chromosome analysis revealed a 46,XY karyotype, using a technique of analysing peripheral leukocytes (50 metaphase cells counted). Hormonal tests showed euthyroidism and morning hyperprolactinaemia with normal daily profile of prolactin. Chorionic gonadotropin subunit β and α-fetoprotein serum concentrations remained within normal limits (1.28 mIU/ml [normal range: 0–5 mIU/ml] and 1.51 IU/ml [normal range: 0–7 IU/ml], respectively). The bone age was assessed as 14–15 years according to the Greulich & Pyle method. After completing a detailed assessment, the patient was qualified for a laparoscopic bilateral gonadectomy. Postoperative histopathological examination revealed gonadoblastoma within the right dysgenetic gonad and the foci of gonadoblastoma in the left gonad. No structures characteristic for ovarian or testicular tissue were found. The patient is currently under constant observation in an outpatient setting. The patient is currently receiving transdermal oestradiol replacement therapy to prevent hypoestrogenism and will begin administration of progesterone preparation. The patient was informed about vitamin D deficiency prevention and adequate calcium supplementation.

The parents of the patient signed written informed consent for the publication of this case report.

Case report

A 15-year-old girl was admitted to the Department of Child Endocrinology due to primary amenorrhoea. The girl’s medical history included birth from the first pregnancy, by vaginal delivery at 40 weeks of gestation with a birth weight of 3920 g, body length of 60 cm, and Apgar score of 10 at five minutes. The child’s psychomotor development was normal. Until admission she did not require hospitalisation or specialist treatment. A growth spurt had been observed about 1.5–2 years before admission. Breast enlargement had been noted a year before admission. The family history was irrelevant. The girl’s mother experienced menarche at 15 years of age.

Upon admission to the Department of Child Endocrinology the patient was in good general condition. In the physical examination obesity (the body weight of 89 kg [> 97c] and the height of 171.4 cm [> 97c], body mass index [BMI] = 30.3 kg/m²) and stretch marks on the thighs were noted. The development of breasts was of Tanner stage B4 and pubic hair of Tanner stage P4. No apparent abnormalities within external genitalia or other evidence of virilisation were observed. Laboratory findings revealed normal biochemistry. Hormonal tests were as follows: hypergonadotropic hypogonadism with low level of oestradiol and testosterone (follicle stimulating hormone 48.68 mIU/ml, luteinising hormone 25.79 mIU/ml, oestradiol 16.79 pg/ml [ranges shown in Table 1], testosterone 14.21 ng/dl [normal range: 6-86 ng/dl]). Pelvic ultrasound revealed a uterus that showed modest oestrogenisation, which was, however, insufficient to make the endometrium visible. No ovaries were found. In the projection of a right gonad a solid structure with a vague ultrasound image was found. To verify the results of the ultrasound examination, magnetic resonance imaging was performed – the uterus dimensions were appropriate for the age (6.0 × 1.8 × 3.2 cm). In the left gonad projection, a small structure with vesicles up to 3 mm was visible. The right gonad was not visible, while a 7 mm thick tissue lesion was found in that area. Fallopian tubes were present. In the right lower abdomen, a structure of unknown origin and with dimensions of 22 × 14 × 15 mm was visible. In the course of further diagnostic tests, the chromosome analysis revealed a 46,XY karyotype, using a technique of analysing peripheral leukocytes (50 metaphase cells counted). Hormonal tests showed euthyroidism and morning hyperprolactinaemia with normal daily profile of prolactin. Chorionic gonadotropin subunit β and α-fetoprotein serum concentrations remained within normal limits (1.28 mIU/ml [normal range: 0–5 mIU/ml] and 1.51 IU/ml [normal range: 0–7 IU/ml], respectively). The bone age was assessed as 14–15 years according to the Greulich & Pyle method. After completing a detailed assessment, the patient was qualified for a laparoscopic bilateral gonadectomy. Postoperative histopathological examination revealed gonadoblastoma within the right dysgenetic gonad and the foci of gonadoblastoma in the left gonad. No structures characteristic for ovarian or testicular tissue were found. The patient is currently under constant observation in an outpatient setting. The patient is currently receiving transdermal oestradiol replacement therapy to prevent hypoestrogenism and will begin administration of progesterone preparation. The patient was informed about vitamin D deficiency prevention and adequate calcium supplementation.

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Discussion

Complete gonadal dysgenesis (CGD) – Swyer syndrome – was described for the first time in 1955 by G. Swyer [11]. Characteristic features of this disorder are as follows: female phenotype, male karyotype, unambiguously female external genitalia, delayed puberty, and the presence of müllerian structures with streak gonads [1, 11]. The affected person usually
has a tall stature, which may be caused by the effect of the Y chromosome or delayed epiphyseal closure due to the deficiency of sex steroids [1]. Generally, due to the absence of hormonal activity of ovaries, there is no appearance of breast development and menarche. Usually, this disorder is identified in adolescence, during the diagnosis of primary amenorrhoea and delay in pubertal signs [12].

The most relevant aspect of this article is the presence of breast development in a girl with Swyer syndrome, which could mask gonadal dysgenesis and delay the diagnosis. According to the best of our knowledge, spontaneous breast development in patients with 46,XY CGD was reported in isolated cases [6, 10, 13–17]). However, the breast development was not adequate in all the reports and did not achieve T Tanner stage V, as in our patient. Catli et al. reported a case of a 46,XY CGD teenager with adequate breast development and irregular menstrual periods [6]. There has also been a case of Swyer syndrome reported with adequate development of secondary sexual features and secondary amenorrhoea [10]. Meyer et al. reported a case of a female with primary amenorrhoea, well developed breasts and one spontaneous vaginal bleeding event [17]. Usually, it is believed that the hormonal activity of tumours within the dysgenetic gonad is responsible for the stimulation of breast development. Fukamatsu et al. [18] reported a case of gonadoblastoma secreting male and female sex steroids. In such a case, virilisation is possible if mainly androgens are synthesised. However, when oestrogen synthesis dominates, female secondary sexual characteristics develop [18–21], although it should be kept in mind that breast development in patients with Swyer syndrome is not always evidence of gonadal malignancy [10, 15]. A case of CGD with spontaneous breast development despite low oestriol level, clinical features of hypogonadism (i.e. osteoporosis) and no gonadal tumours were also described [15]. Hypotheses concerning the origin of oestrogens in girls who suffer from Swyer syndrome say that the production of female sex hormones is possible through the streak gonads. In such a case they can be a source of oestrogen and the reason for adequate breast development [6, 10, 15]. An overlap between non-mosaic Swyer syndrome with 46,XX/46,XY mosaicism is very rare. In this variant, more gonadal functions have been retained and patients are virilised [1]. Moreover, peripheral conversion of androgens to oestrogens and an increased sensitivity of breast tissue to oestrogens are also possible [6, 10, 15]. In such cases, allegedly correctly progressing puberty may delay the diagnosis. It seems that in the analysed case, the aforementioned mechanisms (production of oestrogens through the streak gonads, peripheral conversion of androgens, and an increased sensitivity of breast tissue to oestrogens) could have led to the breast development.

In physiological development, expression of the sex determining region Y (SRY) gene located on the Y chromosome, initiates a genetic cascade that causes the undifferentiated gonad to develop as a testis. In case of improper expression of this fragment, the testes do not develop and the Müllerian ducts persist

| Table I. Normal ranges of gonadotropins and oestradiol |
|-------------------------------------------------------|
| Patients’ results | Normal range |
|-------------------|--------------|
| **LH**            | Follicular phase | 2.4–12.6 mIU/ml |
| 25.79 mIU/ml      | Ovulation     | 14.0–95.6 mIU/ml |
|                   | Luteal phase  | 1.0–11.4 mIU/ml |
|                   | Postmenopausal| 7.7–58.5 mIU/ml |
| **FSH**           | Follicular phase | 3.5–12.5 mIU/ml |
| 48.68 mIU/ml      | Ovulation     | 4.7–21.5 mIU/ml |
|                   | Luteal phase  | 1.7–7.7 mIU/ml |
|                   | Postmenopausal| 25.8–134.8 mIU/ml |
| **Oestradiol**    | Follicular phase | 12.5–166 pg/ml |
| 16.79 pg/ml       | Ovulation     | 85.8–498 pg/ml |
|                   | Luteal phase  | 43.8–211 pg/ml |
|                   | Postmenopausal| <5.0–54.7 pg/ml |

FSH – follicle stimulating hormone; LH – luteinising hormone
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Table II. Diagnosis of primary amenorrhea [26, 27]

| Pregnancy test serum TSH and PRL level | Pregnancy test positive, abnormal TSH or PRL levels | Treat as appropriate |
|---------------------------------------|----------------------------------------------------|---------------------|
| FSH and LH levels                     | Low                                                | Functional hypothalamic amenorrhea |
|                                       |                                                    | Constitutional delay of puberty |
|                                       |                                                    | Primary GnRH deficiency |
|                                       |                                                    | Anorexia nervosa |
|                                       | Normal                                             | Outflow tract obstruction |
|                                       |                                                    | Late onset of CAH |
|                                       | Elevated                                           | Hypergonadotropic hypogonadism |
|                                       |                                                    | (karyotyping analysis needed) |
| Oestradiol                            | Low                                                | Poor ovarian function |
| USG imaging                            | Absent or abnormal uterus                          | Karyotyping analysis needed |
|                                       | Normal uterus                                       | Outflow obstruction |
| Karyotype                              | 46,XX + hypergonadotropic hypogonadism             | Premature ovarian insufficiency/failure |
|                                       | 46,X + hypergonadotropic hypogonadism              | Turner syndrome |
|                                       | 46,XX + absent or abnormal uterus                  | Müllerian ducts agenesis |
|                                       | 46,XY + absent or abnormal uterus                  | Androgen insensitivity |
|                                       |                                                    | Swyer syndrome |
|                                       |                                                    | 5α-reductase deficiency |
| AMH                                   | Elevated                                           | Functional hypothalamic amenorrhea |
|                                       | Low                                                | PCOS |
| Free testosterone levels, DHEA-s      | Elevated (urinary steroid profile analysis should be considered) | Hyperandrogenism |
|                                       |                                                    | PCOS |
|                                       |                                                    | Ovarian or adrenal tumour |
|                                       |                                                    | CAH |
| Oestradiol                            | Low                                                | Cushing syndrome |
|                                       |                                                    | CAH |

TSH – thyroid-stimulating hormone; PRL – prolactin; FSH – follicle stimulating hormone; LH – luteinising hormone; GnRH – gonadotropin-releasing hormone; CAH – congenital adrenal hyperplasia; AMH – anti-müllerian hormone; PCOS – polycystic ovary syndrome

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sia (CAH) (from deficit of the 17α-hydroxylase/17–20 lyase enzyme), and complete androgen insensitivity syndrome (CAIS) should be considered in the differential diagnosis [17, 25]. Deficiency of 17α-hydroxylase/17–20 lyase is a rare form of CAH, caused by loss-of-function mutations in CYP17A1. It appears in adolescence or in adult life. XY children with this form of CAH develop female phenotype; however, they have a histologically normal testis. Due to the accumulation of mineralocorticoids, a characteristic symptom in these patients is difficult-to-treat hypertension [17, 26]. Patients with CAIS are phenotypically female with female gender identification. Gonads are found high in the inguinal canals or in the pelvis, and müllerian structures are absent. Hormonal tests usually show elevated oestrogen and androgen levels [5, 25]. The androgen insensitivity is caused by the androgen receptor mutations [2]. Table II shows the diagnostic tests in cases of primary amenorrhoea [26, 27].

Because of the possibility of neoplasm transformation in patients with 46,XY karyotype and dysgenetic gonads, bilateral gonadectomy should be performed as soon as the diagnosis is made [1, 4, 5, 7, 10, 19, 22, 28]. According to various authors, the occurrence of tumours in Swyer syndrome varies from 15% to as much as 55% of cases, with the incidence increasing with age [1, 4, 11, 20]. Among all DSD, in patients with 46,XY CGD the tumour presence and malignancy risk are the highest. Therefore, Swyer syndrome is considered the most threatening disorder [4]. The most common tumours include gonadoblastoma and dysgerminoma. Gonadoblastoma almost always develops in DSD with the presence of Y chromosome material, and more than 80% of cases involve patients with a female phenotype [20]. Gonadoblastoma is a tumour originating from persistent undifferentiated cells of a dysgenetic gonad. Its development is associated with the expression of the testis-specific protein, Y-linked gene (TSPY), and with the presence of SRY, SOX9, and WT-1 mutations [1]. Despite being a benign tumour, it may progress further and could be a precursor to malignant germ cell malignancy – usually dysgerminoma [1, 4, 19, 20, 28]. It is estimated that half of gonadoblastoma will have malignant transformation [5]. The tumour can be uni- or bilateral. There have also been reported cases of concomitant occurrence of gonadoblastoma and dysgerminoma within one gonad [11]. Diagnosis is made most often in the pubertal age. However, a case of a three-month-old child with mixed gonadal dysgenesis and concomitant gonadoblastoma has been described [28]. If gonadoblastoma is diagnosed, the prognosis is very good. However, if the features of malignant transformation are found, then the survival rate decreases [20].

Patients with CGD are always reared as female, according to the phenotypic sex, and are unlikely to have gender dysphoria [5, 12]. The case of the described patient was similar. However, psychological care is advisable [4]. Moreover, patients with 46,XY and gonadal dysgenesis require sex hormone treatment. It helps to induce and maintain adequate breast development and menstruation, and to achieve an optimal peak bone mass. For this purpose, oestrogen and progesterone supplementation is used until menopausal age [1]. Despite the lack of female gonads, pregnancy is possible because these patients have normal müllerian structures; it is possible via ova donation and in vitro fertilisation. Because of the genetic background of Swyer syndrome, familial screening should be considered [11, 19].

In conclusion, phenotypic female 46,XY DSD is a rare disorder, diagnosed most often in adolescence. Our observation underlines the need to consider DSD 46,XY in the presence of primary amenorrhoea, even when pubertal development is present. Normal breast development may mask gonadal dysgenesis and delay diagnosis. It has to be kept in mind that germ cell tumours have a tendency to grow and metastasise rapidly. Delayed diagnosis may increase the risk of malignant transformation and cause a poor diagnosis and reduced survival rates. In the described case, genetic analysis did not reveal any of the known mutations connected with CGD. Despite that, prophylactic gonadectomy was performed due to the high risk of malignancy in every case of 46 XY with gonadal dysgenesis. Early sex hormone treatment helps to induce and maintain typical pubertal and psychosexual development, and to achieve an optimal peak bone mass.

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