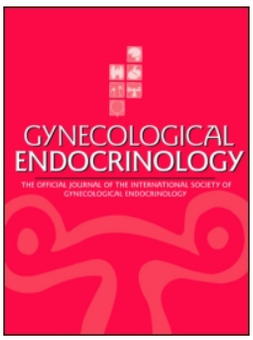

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CASE REPORT

POI after chemotherapy and bone marrow transplant may mimic disorders of sexual differentiation – a case report of a patient with primary amenorrhea and 46, XY karyotype

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ABSTRACT

Cytogenetic examination may be useful in determining the reason for primary amenorrhea in phenotypically female patients. The result 46, XY usually indicates two syndromes: complete androgen insensitivity or pure gonadal dysgenesis. We report a case of a patient, who due to acute lymphoblastic leukemia in childhood was treated with total body irradiation and bone marrow transplantation. Later on the patient presented with symptoms typical for premature ovarian failure and male karyotype in peripheral lymphocytes. The cytogenetic examination for peripheral cells showed normal female karyotype. Therefore, it has been concluded that ovarian function impairment resulted rather from the gonadotoxic effect of oncological treatment than as a disorder of sexual differentiation. The survival rates of childhood cancer are very high and some of the patients will experience premature ovarian failure. It must be remembered that after bone marrow transplantation karyotype of peripheral lymphocytes may be misleading.

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Primary ovarian failure; acute lymphoblastic leukemia; bone marrow transplantation; disorders of sexual differentiation

Introduction

Primary amenorrhea is, according to the most recent consensus, a condition defined as an absence of menarche stated at the age of 15 or three years after thelarche [1]. It may appear as a sign of various disorders including impairment of the ovaries, the hypothalamus or pituitary gland, anatomical abnormalities within the genitourinary tract and metabolic or endocrinologic disorders [2]. Therefore differential diagnostic should consist of establishing past medical history, performing a gynecological examination, marking full hormonal profile and determining the patient's karyotype. The recent may be the decisive measure in some chromosomal abnormalities, allowing to exclude Turner Syndrome (46, XO) and other disorders of sexual differentiations. 46, XY karyotype is not a common result in phenotypically female patients presented with primary amenorrhea [3,4]. In female individuals with 46, XY genotype prophylactic gonadectomy is required because of the high prevalence of gonadal tumors [5]. Oncological treatment during childhood may also lead to primary amenorrhea due to gonadotoxic effect of chemotherapy and irradiation.

We present a case report of childhood cancer survivor patient with primary amenorrhea, whose lymphocytes karyotype result (46, XY) could have wrongly directed the diagnosis toward disorders of sexual differentiation.

Case report

A 24-year-old woman was admitted to the Department of Gynecological Endocrinology suspected of premature ovarian insufficiency (POI). Her past medical history revealed chemotherapy because of acute lymphoblastic leukemia (ALL) when she was 7, with a late relapse and total body irradiation followed by bone marrow transplantation at the age of 12. On admission, she reported to be free of the disease and did not take any medication because of leukemia. As an adolescent, the patient noticed a lack of menstrual flow and was presented with poor secondary sex characteristics to the pediatric department. Initially, she was prescribed estrogen supplementation (2 mg/day orally). Later progesterone was added to induce withdrawal bleeding. First menstruation occurred at the age of 18, but was only achieved by hormonal therapy (2 mg/day estradiol valerate with 0.5 mg norgestrel for 10 days in the month), which she continued since then and overdrew 6 months prior to consultation in the clinic. The clinical manifestation was suggestive of impairment of the ovarian tissue by the chemotherapy, which is consistent with the development of POI.

On admission, she was assessed as a stage V according to the Tanner scale. Gynecological examination and transvaginal ultrasound, determined the presence of vaginal canal and Müllerian derivatives, small ovaries and normal female external genitalia. The uterus was also small with a thin 4 milimeter endometrium. Laboratory data showed diminished concentration of estradiol (<10 pg/ml) and increased levels of serum follicle-stimulating hormone FSH and luteinizing hormone LH (73.62 mIU/ml and 35.57 mIU/ml, respectively). Anti-Müllerian hormone (AMH) concentration was very low (<0,01 ng/ml). The rest of the results including levels of basal thyroid hormones, TSH, cortisol, prolactin, glucose tolerance test and lipids profile were within the referenced range. Patient's lymphocytes karyotype turned out to be

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46, XY. Such a result was more suggestive of a disorder of sexual development resultant from gonadal dysgenesis rather than exclusive gonadotoxic impact of chemotherapeutics and irradiation in childhood and should have prompted considering prophylactic gonadectomy in the light of the high risk of tumors.

Repeated analysis of the case, revealed the fact, that the patient had an allogenic bone marrow transplant from an unrelated male donor. Another sample, this time containing fibroblasts (swab from the cheek) was taken and the karyotype was reassessed. It appeared to be 46, XX.

The patient remained diagnosed with iatrogenic premature ovarian insufficiency. The treatment of the patient required resumption of estradiol and progestogen substitution without the need for prophylactic gonadectomy. The patient remains on hormonal therapy (2 mg estradiol valerate orally every day with 0.5 mg norgestrel for 10 days a month) and attends the outpatients clinic for regular checkups.

Discussion

Premature ovarian insufficiency affects around 1% of women under the age of 40. It is caused by ovarian function depletion and presents as oligo- or amenorrhea for at least four months and FSH level over 25 IU/ml, checked twice at least four weeks apart [6]. When serious ovarian function deterioration takes place in childhood, the patients experience primary amenorrhea.

Performing karyotype examination is a crucial tool in excluding any chromosomal abnormalities such as 46, XO; 46, XY; 46, XY/46, XX accompanied by lack of menstruation.

In tertiary centers, the percentage of 46, XY karyotype in females with primary amenorrhea, either with pure gonadal dysgenesis or complete androgen insufficiency syndrome (CAIS) may reach 3.4–6.8% [3,4]. Despite the rarity, those rare conditions should be excluded due to increased risk of tumors such as dysgerminoma or gonadoblastoma.

Pure or complete gonadal dysgenesis, also known as Swyer syndrome may be recognized if despite male karyotype, testes do not differentiate normally. Such condition may be explained by mutation in several genes responsible for gonadal development including ARX, ATRX, CBX2, DHH, DMRT1, GATA4, MAMLD1, MAP3K1, NR0B1, NR5A1, SOX9, SRY, WNT4, WT1, and WWOX, from which SRY appears to be the most significant and commonly alleged in the literature, accounting for 10–20% cases [7]. Affected individuals are typically tall-statured, with female external and internal genitalia and features of hypoestrogenism (such as lack of breast development, amenorrhea, increased osteoporosis and cardiovascular risk). Laboratory findings show hypergonadotropic hypogonadism with low levels of serum testosterone and AMH [7].

Complete androgen insensitivity syndrome is a condition, in which testes are developed and their hormonal function is preserved, nevertheless peripheral tissues are resilient to testosterone due to mutation in gene encoding androgen receptor (AR). Absence of testosterone activity, thus the conversion of its excess to estrogens provides the presence of external female phenotype, normal presence of breast development and external genitalia (beside shorter vagina). In such individuals, Müllerian derivatives are not preserved due to the regression of a duct induced by AMH produced by functional gonads. Testes may be situated either in the abdominal cavity or throughout the inguinal canal or in the labia majora. In two recent localizations, they may be palpable and in the canal, they may be the source of the inguinal hernia. Hormonal profile consists of elevated testosterone and detectable estrogen concentrations [8].

The phenotype in our patient (normal external genitalia, presence of Müllerian derivatives) accompanied by hypogonadotropic hypogonadism and low testosterone serum concentration in blood tests with the coexistence of 46, XY karyotype advocated for diagnosing a patient with Swyer syndrome. The presence of well developed secondary sexual characteristics, not frequently encountered in gonadal dysgenesis, could have been explained by the administration of hormonal replacement therapy since adolescence.

In the cancer survivor patients, we may face another clinical problem, which is the insufficiency of the ovaries after oncological treatment. Gonadal toxicity may be caused by the use of chemotherapeutics or radiotherapy. Most potent gonadotoxic effect is credited to alkylating agents, which are frequently administered during leukemia treatment (e.g. cyclophosphamide). Total body irradiation used before bone marrow transplantation exposes the ovaries to radiation in the dose of 12 Gy, what is associated with high risk of gonadal failure in every age group [9,10]. The prevalence of premature ovarian failure in cancer survivors may reach 10.9% [11].

We performed karyotype examination on lymphocytes as a routine diagnostic measure in primary amenorrhea in the cancer survivor patient, whose signs were also consistent with the manifestation of Swyer syndrome. However, in the presented case the karyotype of peripheral lymphocytes was changed for 46, XY one due to bone marrow transplantation from unrelated male donor not by a disorder of sexual differentiation. We have found a similar case reported by Huang and Tian, in which a female patient received bone marrow transplant from her brother [12]. The authors also admitted to similar misdiagnosis. That situates a problem described above as an important diagnostic pitfall. Especially, when we consider that with currently used treatment modalities, the survival rate of childhood ALL reaches nowadays even about 85–90% [13].

Conclusion

This is a case report of a patient with primary ovarian insufficiency caused by the treatment of acute lymphoblastic leukemia during childhood, whose karyotype of peripheral lymphocytes turned out to be 46, XY. Male genotype was resultant from bone marrow transplant from male donor rather than inborn defect followed by disturbance in gonadal determination. In the light of higher efficacy of leukemia treatment and wider application of bone marrow transplant, we may presume that such misdiagnoses may take place more often in the future and aware among gynecologists about false positive results of cytogenetic examination in cancer survivals should be raised. Although, the cancer survivors experience POI mainly due to chemo- and radiotherapy, they should be screened for all the other reasons of ovarian function depletion. However, a gynecologist should be aware that the karyotype of peripheral lymphocytes may be misleading after bone marrow transplantation.

Disclosure statement

The authors report no conflict of interest.

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